Survivorship Care for Cancer Patients

A Clinician's Handbook

Stefan Rauh
Editor

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A very warm hug goes to a wonderful empowered cancer survivor, Nathalie (my wife), as well as her "informal caregivers" Adrien and Lea (our children) – and many friends who have proven so very supportive and helpful.

Stefan Rauh

Introduction

In 2020, there have been close to 3 million new cancers diagnosed in Europe, and 1.3. million deaths due to cancer. More than one out of three citizens facing the diagnosis during his lifetime. A majority of patients (62%) is at least 65 years old at diagnosis [1].

Over time, mortality rates have decreased due to advances in detection and treatments – and will hopefully continue to do so in the future. It is estimated that there was a 5% decline in overall mortality from 2015 – 2020, with particularly important better outcomes in breast, prostate and gastric cancers for most countries of the European Union [2]. Half of those diagnosed with cancer may today expect to live 10 years or longer [3]. These are excellent news, but for cancer patients, the good news does not come alone. Cancer survivors face sequelae from their malignant disease as well as treatment -related effects and co-morbidities, which may or may not wane off over time. In addition, they face challenges such as maintaining or restoring their psycho social relationships, keeping up with credits and costs of living and getting back to work, just to name some.

I am a medical oncologist and have started to train in 1991. Compared to today, treatments were often badly tolerated, and did not necessarily achieve long survivals. Those "who made it", the survivors, were not in the main focus of a busy oncologist's work schedule, apart from regular recurrence screening. As time went by, as more of my patients came back for longer follow-up periods – and more and more expressed their needs beyond the confirmation to stay in remission, I have gained awareness concerning the need for true survivorship care and its complexity. This has also led to an enriching experience around a survivorship patient guide in 2017 [4].

Survivorship has already been identified a major challenge in 1985 [5]. The concept of survivorship care has been proposed for implementation into every cancer patient's journey as of 2006 by the American Institute of Medicine (IoM) [6]. But even in 2021, 15 years after IoM's call for action, much has still to be done. Throughout Europe, there is no common approach to survivorship care, worse: Conceptual survivorship care is still even absent in many places. There is still much to be known about the optimal survivorship care through dedicated research.

This handbook's aim is to provide a manual for clinicians, which should give a detailed overview of the multiple aspects of contemporary survivorship care. You should also be able to use it as a manual to look up a specific chapter for your daily

needs or to construct or further develop your local survivorship care project (this is also the reason why some chapter introduction may have redundant features).

I am very grateful to all my wonderful and great co-authors of this handbook.

I hope you will find whatever information and inspiration you need for your daily work with cancer survivors.

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Definition of Survivorship Care

1

Florian Strasser

Definition of Survivorship Care

The number of humans confronted with cancer disease and cancer treatments is increasing rapidly and steadily, also associated with the evolution of modern oncology. To accompany these human fellows to live the best possible and happy lives, common definitions of survivor, cancer survivorship, and survivorship care may serve to coordinate initiatives.

Evolution of Term in Pubmed

The first article in Pubmed mentioning the term "cancer survivors" was in 1947 (Pubmed articles with the term cancer start from 1784). The focus of approx. 1400 papers until 1985 were on 5-year survivors and atomic bomb survivors tackling frequencies of relapsing tumors and secondary neoplasm. From the late 70s, the focus widened with publications describing long-term toxicities and functional impairments however mainly addressing the population of survivors of childhood cancer. The term "cancer survivorship", in contrast to the term survivor, yielded two papers from 1956 to 1985, until March 2021 approx. 3000 papers. The term "survivorship *care*" and cancer appeared in 2002, with approx. 1400 papers until March 2021. Both terms together yield 3750 papers, with 50% of papers published since 2018 and over 99.99% after 1985. That means that "cancer survivorship" and "survivorship care in cancer" are overlapping but not identical terms blooming after 1985.

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Brief History

The distinct birth of "cancer survivorship" may be in 1985, when a physician wrote about his experiences being a cancer patient undergoing the trajectory of a cancer patient from diagnosis to anticancer treatment to being tumor-free but not free of sequelae. Dr. Mullan wrote, "Seasons of Survival: Reflections of a physician with cancer" [1]. One year later, in 1986, the National Coalition for Cancer Survivorship (NCCS) [2], a cancer advocacy group was founded with Dr. Mullan as one (prominent) founding member [3]. In 1996 NCI established an Office of Cancer Survivorship (OCS).

Another milestone was the 2006 report of the Institute of Medicine (IOM) and National Research Council written by the Committee on Cancer Survivorship ("lost-in-transition") [4], with a preparatory period of a few years, commented by Renee Twombly 2004 [5]. The Cancer Journal dedicated in 2008 a full issue (Vol. 14 Issue 6) on Cancer Survivorship, lead by the guest editor Kenneth D Miller [6]. He and others reflected about Mullans' seasons, which they propose shall be revisited [7]. One reason for clarification was the importance to strengthen the collaboration of primary care and specialist oncologist providers, as summarized in 2010 by Grunfeld and Earle [8]. In 2012, the American Cancer Society (ACS) published a concept of various characteristics of cancer survivors. The NCCN published in 2014 Guidelines on Cancer Survivorship [9]. Surbone and Tralongo, 2016 [10], supported the importance of categorizing cancer survivors (acute vs chronic vs long-term vs healed), building on own [11, 12] and others work [13] requesting a change of culture and focused interventions. The year 2016 was the Anniversary of three milestones: 30 years NCCS, 20 years NCI-OCS, and 10 years of the IOM-Report Lost-in-Transition. Nekhlyudov L et al. summarized in 2017 these anniversaries and discussed critically and hopeful the progress made on the 10 IOM recommendations in the last decade [14]. Again, the importance of categorization of cancer survivors by risk-stratification was subsequently debated [15, 16]. Also in 2017 a systematic review summarized and discussed all available definitions on who is a cancer survivor [17]. The European Society Medical Oncology (ESMO) launched in 2017 together with the European Cancer Patient Coalition (ECPC) and the International Psycho-Oncology Society (IPOS) a Patient Guide on Survivorship [18]. In 2018, Park et al. emphasized the importance of categorization on the grounds of different patients' needs at different phases of illness [19]. Also in 2018, Charles Shapiro wrote a landmark review in the NEJM on cancer survivorship [20]. The ESMO discussed in 2018 palliative and supportive in a position paper [21], emphasizing "patient-centered care" including key issues and interventions delivered by various (supportive or palliative) services, focusing on integration and collaboration, not on separation. Survivorship care was in this position paper not specifically defined but a natural and self-evident component of excellent patient-centered care. Likewise, MASCC (Multinational Association of Supportive Care in Cancer) [22] mentions the survivorship phase, but does understand the issue needs-based without an own sharp definition. In 2019, a well-renowned oncologist experienced metastatic (prostate) cancer and advocates—together with another patient living with metastatic sarcoma, the fourth tumor in her life—to perform research and develop clinical programs to tackle key issues in *metastatic* cancer survivorship [23]. The term metasurvivorship was proposed by one group of authors from the US,

supported by a conceptual framework [24]. Early integrated cancer palliative care offers needs-based therapeutic and networking interventions for patients dealing with metastatic cancer disease [25]. The suitability of the application of key palliative care principles (focus on QoL, biopsychosocial symptom management, holistic perspective of the illness experience) on survivorship care was discussed in 2021 [26], also other authors emphasized the potential of palliative care competencies in survivorship care [27].In 2021 NCI published the results of a workshop held in 2019, which convened cancer survivorship researchers, advocates et al. for a 1 day meeting, followed by consultation of the wider survivorship community to identify evidence gaps and research priorities [28]. NCI acknowledges a need for expanded research on metastatic survivorship [29]. Currently, emphasis is given to research (see above), personalized survivorship care pathways [30], and survivorship care plans [31]. Also, the oncology community demands the routine integration in survivorship issues in cancer-specific guidelines. ESMO describes in the Guidelines Methodology under Standard Operating Procedures on paragraph 4.4.6 Follow-up, long-term implications and survivorship that "recommendations for patient follow-up and information on long-term toxicities of [anticancer] treatment, second tumours, psychosocial implications, rehabilitation and any other issues related to survivorship" shall be emphasized [32]. Several ESMO supportive and palliative care guidelines [33] tackle survivorship-specific issues, but ESMO does not provide (by March 2021) a specific "survivorship guideline."

In summary, the history shows, that increasingly patient needs getting recognized, characterization of different patient situations guide tailored interventions and that routine integration of survivorship issues in cancer-specific guidelines may contribute to more awareness among oncology professionals.

Definitions

Until 1985 the usual definition of "cancer survivor" was "someone who had been free of any sign of the disease for five years." People who were not "cancer survivors" were often called "cancer victims." This definition did not take into account symptomatic or psychosocial issues but applied Battlefield or violence victim's analogy.

The initial concept for survivorship of Dr. Mullhan 1985 included bio-medical (e.g., secondary tumors, long-term effects of [anticancer] treatment, rehabilitation, reproductive health, and long-term health maintenance) and psychosocial (e.g., community acceptance of cancer patients, insurance discrimination, barriers to employment, education of youth about cancer). Interestingly (from a 2021 perspective) the author did not mention psychosocial issues such as fear of recurrence, post-traumatic distress and growth, social withdrawal, and depression. He proposed already three different survivor-periods, which he called ***seasons of survival***:

- **Acute** survival (diagnosis and initial anticancer treatment).
- **Extended** survival (watchful waiting and surveillance, maybe maintenance treatment).
- **Permanent** Survival (long-term remission).

These three seasons are characterized by different sets of patient needs.

The **"acute survival"** starts at the diagnosis of the cancer disease. The main challenges arise from diagnostic and therapeutic interventions. Patients experience anxiety, trauma, and uncertainty, important and also constant features of this phase.

The **"extended survival"** begins when the patient has finished the initial anticancer treatment, often delivered in an intensive way. In this phase, active surveillance may take place including repeated diagnostic interventions or also maintenance or consolidation anticancer treatment. In this phase (or season) fear of recurrence is an, if not to say "the" key emotion. Patients also experience physical limitations associated with side effects/toxicity of anticancer treatments. Deconditioning, fatigue, or specific disabilities are now manifest barriers and challenges in the process back to normal-as-possible life at home, the community, and the workplace.

The "**permanent survival**" is the phase, when the patient is considered as "cured", which means that the likelihood of recurrence is considerably low; however, there is no consensus below which probability of recurrence of the word cured may be applied. Patients experience challenges with employment and insurance but also many issues of long-term survivors such as chronic heart, lung or kidney disease, neurological complications, psychological burden including PTSD, anxiety or depressive reactions, and so on.

The National Coalition for Cancer Survivorship (**NCCS**) [2] is the cancer advocacy group which was founded in 1986 [3] by F. Mullan and others. NCCS defined cancer survivorship as "the experience of living with, through, and beyond a diagnosis of cancer." Another beautiful wording is used:

> From the time of diagnosis and for the balance of life

Important also to NCCS is to state, that there are many types of survivors, including those humans living with cancer and those humans living free of cancer. With this term, it is possible to capture a population of humans with a history of cancer rather than to provide a label that may or may not resonate with individuals. Also, family members, friends, and caregivers are impacted by the survivorship experience too and are therefore included in this definition. This initiative of NCCS to redefine the term survivor was (Quote from NCI) "part of a transformation in how people with cancer talked about their experiences. It provided hope for the newly diagnosed, and empowered patients to be active participants in their care."

The concept of survivorship was further developed in 1989 [34] by the description **of several potential cancer survival trajectorie**s:

- Live cancer-free for many years.
- Live long cancer-free, but die rapidly of late recurrence.
- Live cancer-free (first cancer), but develop second primary cancer.
- Live with intermittent periods of active disease.
- Live with persistent disease.
- Live after expected death.

This broad concept including both the short- and long-term consequences of cancer disease and treatment paved the road to vocalize the cancer survivors' changes in self-concepts and personal horizons, modifications in social relationships, and considerations of costs of treatment and follow-up.

The **NCI**[1] created the phrase "cancer survivorship" to describe (Quote) "*this broad experience on the cancer continuum—living with, through, and beyond a cancer diagnosis.*" It was recognized that the attribution of the posttreatment period was obscured by advances in anticancer treatment, namely adjuvant or (later) maintenance treatments. The consequences of cancer screening further complicate the definition of survivor.

NCI adapted its 2004 definition of cancer survivorship [35] from NCCS as follows:

> "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life." Family members, friends, and caregivers are also impacted by the survivorship experience and are therefore included in this definition.

The *landmark* **Committee on Cancer Survivorship** report (limited to adult cancer) from the **IOM** (Institute of Medicine) and National Research Council [4] in **2006** recognized that (Quotes) "*The transition from active treatment to posttreatment care is critical to long-term health*" and "*the importance of addressing unmet needs of the large and growing number of cancer survivors during this phase of care.*" Concerning the survivors' needs the committee states (Quote): "*Although the population of cancer survivors is heterogeneous, with some having few late effects of their cancer and its treatment, others suffer permanent and disabling symptoms that impair normal functioning. Psychological distress, sexual dysfunction, infertility, impaired organ function, cosmetic changes, and limitations in mobility, communication, and cognition are among the problems faced by some cancer survivors.*"

As definition, the IOM-committee applied the NCI 2004 definition (see above). In addition, the IOM-committee elaborated, based on the President's Cancer Panel 2004, on the issues around "***who is a Cancer Survivor***" as follows (Quotes):

> *Among health professionals, people with a cancer history, and the public, views differ as to when a person with cancer becomes a survivor. Many consider a person to be a survivor from the moment of diagnosis; in recent years, this view has become increasingly prevalent. Some, however, think that a person with a cancer diagnosis cannot be considered a survivor until he or she completes initial treatment. Others believe a person with cancer can be considered a survivor if he or she lives 5 years beyond diagnosis. Still others believe survivorship begins at some other point after diagnosis or treatment, and some reject the term "survivor" entirely, preferring to think of people with a cancer history as fighters, "thrivers," champions, patients, or simply as individuals who have had a life-threatening disease. A considerable number of people with a cancer history maintain that they will have survived cancer if they die from another cause.*

[1] https://cancercontrol.cancer.gov/ocs/ 2014

In essence, the definition shall cover a) the individual, personal experience of the human confronted with cancer disease and anticancer treatment and b) the understanding that a cancer survivor, and also proxies of this human of all kinds, are challenged by and have to deal with many somatic, intellectual, psychological, social, vocational, or existential issues impacting the health and happiness of the person.

The professional approach to address these needs was named Survivorship Care. The IOM-Committee proposed "**Essential Components of Survivorship Care"**

1. **Prevention** of recurrent and new cancers, and of other late effects;
2. **Surveillance** for cancer spread, recurrence, or second cancers; assessment of medical and psychosocial late effects;
3. **Intervention** for consequences of cancer and its treatment, for example, medical problems such as lymphedema and sexual dysfunction; symptoms including pain and fatigue; psychological distress experienced by cancer survivors and their caregivers; and concerns related to employment, insurance, and disability;
4. **Coordination** between specialists and primary care providers to ensure that all of the survivor's health needs are met.

In 2008 Cancer Journal special edition a proposal was made to revise the "seasons of survival" [7], to acknowledge different patient or survivors' needs.

Seasons of Survival Revisited

- **Acute.**
- **Transitional.**
  - transition from active treatment to careful observation and the emotional, social, and medical adaptations that occur.
- **Extended.**
  - Remission maintained: complete remission that requires ongoing therapy.
  - Cancer-Free Permanent: complete remission and with a favorable prognosis.
  - Living with cancer: requiring ongoing treatment for recurrent, active, and often advanced disease.
- **Permanent.**
  - Cancer-free but "not free of cancer."
  - Cancer-free but continue to have significant "fall-out" from cancer and its treatment including psychosocial, medical, financial, or legal sequelae.
  - Development of second cancers which may be unrelated to first cancer or its treatment, or may be more likely due to genetic or environmental factors.
  - Development of cancers that are secondary to the initial treatment.

In the same issue of The Cancer Journal a list of common Long-Term Sequelae of Cancer as "medical issues" was presented [36], highlighting the many—somatic needs of cancer survivors in the various seasons (*list adapted by FS*).

- Cardiovascular.
  - Cardiomyopathy.
  - Valvular heart disease.
  - Coronary artery disease.
- Pulmonary.
  - Pulmonary fibrosis.
  - Interstitial lung disease.
  - Strictures/obstruction.
- Gastrointestinal.
  - Malabsorption.
  - Second malignancies.
- Rheumatologic.
  - Osteopenia/osteoporosis.
  - Osteonecrosis.
- Lymphedema.
- Endocrine.
  - Panhypopituitarism.
  - Hypothyroidism.
  - Adrenal insufficiency.
  - Diabetes mellitus.
- Renal.
  - Chronic kidney disease.
- Sensory/neurologic.
  - Hearing loss.
  - Visual changes.
  - Neuropathy.

Another article in the same issue [37] highlighted psychological and emotional issues experienced by cancer survivors.

Negative psychological reactions in survivors

- Fear of recurrence.
- Overall increased sense of vulnerability.
- Feelings of uncertainty, concern, and worry.
- Post-traumatic stress disorder (often subsyndromal) with symptoms of increased arousal, intrusive thoughts, and avoidance-numbing.
- Decreased sexual activity, interest, or satisfaction.
- Changes in body image and sense of being sexually attractive.
- Site-specific physical side effects and dysfunctions.
  - Discomfort with eating in public (after head-and-neck cancer).
  - Lymphedema.

Positive emotional and psychosocial reactions to having survived cancer.

- Finding meaning and purpose in life.
- Experiencing positive changes in outlook.
- Having an increased sense of spirituality and faith.
- Having greater appreciation in life.

These two lists may be expanded in the era of modern oncology with many forms of available immunotherapy, targeted drugs, and multimodal and sophisticated surgical and radiooncological therapies. However, the key somatic and emotional issues are probably comparable to 2008, most important is to be aware of these issues and act.

The **American Cancer Association** (ACS) also used in 2012 the beautiful NCCS definition:

> A cancer survivor is any person who has been diagnosed with cancer, from the time of diagnosis through the balance of life.

ACS also emphasized the **range of cancer experiences and trajectories**, including:

- Living cancer-free for the remainder of life.
- Living cancer-free for many years but experiencing one or more serious, late complications of treatment.
- Living cancer-free for many years, but dying after a late recurrence.
- Living cancer-free after the first cancer is treated, but developing a second cancer.
- Living with intermittent periods of active disease requiring treatment.
- Living with cancer continuously without a disease-free period.

While the definition of a cancer survivor was more or less consensual (and gave hope to a change in culture [12]), as well as key areas or priorities[2] for survivorship research [38], the importance to **classify** or characterize **cancer survivor populations** was again raised in 2016 [10]. The authors (**Surbone and Tralongo**) argue (Quote): "*a proper categorization of persons now broadly defined as cancer survivors can provide support to risk-based survivorship care, new clinical and organizational approaches, and improved follow-up and surveillance recommendation and guidelines*". Also, "*communication with patients and families and patient adherence to clinical recommendations could be improved, as well as effectiveness of survivorship care in different delivery contexts*". Finally, "*the application of categories of survivorship might help us avoid the infliction of psychological burdens of overmedicalization and potential social stigmatization on some of our patients and foster adequate follow-up, surveillance and global care for others.*"

[2] Gaps in the contemporary study of survivorship: predominance of breast cancer studies, limited research on older survivors, persistent research dearth of long-term (5 years) survivors, lack of intervention studies on young survivors, and areas of deficiency in research objectives, such as biologic or genetic components and care delivery

Categories of Patients with and Survivors of Cancer Category Description

- **Acute** Patients/survivors at first diagnosis or relapse, who require acute intervention.
- **Chronic** Patients/survivors with cancer that slowly progresses or alternates between phases of remission and relapse, often accompanied by acceptable quality of life.
- **Long-term** Patients/survivors in clinical remission for long periods of time or for their entire life, who remain at risk for distant relapse or second tumors and who potentially can experience late treatment-related medical and psychosocial sequelae.
- **Cured** Disease-free patients/survivors whose cancer-specific mortality and life expectancy years after years diagnosis equal that of sex- and age-matched members of the general population.

This proposal of acute, chronic, long-term, and cured categories is both a simplification (compared to ACS 2012 and seasons of survival revisited 2008) in four categories and a specification, compared to just "one" type of cancer survivor. However, the patients living with incurable, metastatic cancer disease are not well picked up in these four categories. In the state-of-the-art review in NEJM 2018 by Shapiro, he focuses also mainly on long-term and cured survivors with their needs and burdens, emphasizing explicitly the older population and the childhood cancer survivors [20].

The importance to categorize cancer survivors better who live with (incurable, metastatic) cancer as own category was raised in 2018 by authors representing the oncology, hematoncology, supportive and palliative areas of modern oncology in their article "**Shades of Survivorship.**" The key point is to guarantee adequate awareness of supportive and palliative needs of these cancer survivors and the reduction of confusion around prognosis. The authors argue that patients living with cancer may feel psychological pressure to (Quote) "*embody the term survivor and perpetuate an image of strength, which may conflict with their feelings and perspectives on their disease.*" Also, the authors state that (Quote) "*Patients receiving active cancer therapy and those living with cancer may feel ambivalent about being labeled a survivor.*"

Shades of Survivorship Describes Three Categories

- Patients newly diagnosed receiving active therapy with curative intent.
- Patients who have completed active therapy with curative intent (on or off maintenance therapy).
- Patients living with cancer.

These three (Quote) "*more nuanced terms to describe patients during these phases may provide a more realistic and individualized approach to addressing these needs*" and "*would honor and capture the essence of their experiences.*"

Supportive and palliative care needs of patients in the three categories[3]	
Patients newly diagnosed Receiving active therapy with curative intent	Treatment of ***symptom burden*** due to cancer and acute side effects of therapy (e.g., nausea, anxiety, fatigue, diarrhea, and infections) Help with substantial (existential) ***distress*** associated with a new diagnosis of cancer disease ***Coordination support*** for frequent visits with oncology and adjustment to treatment schedule and work schedule changes ***Communication*** focused on understanding illness and anticancer treatment and on (initial) decision-making process
Patients who have completed active therapy with curative intent (on or off maintenance therapy)	Treatment of ***symptom burden*** due to long-term side effects of cancer therapy (e.g., fatigue, menopausal symptoms due to hormonal therapy, weight gain, changes in bowel or bladder function, and cognitive dysfunction) Support for dealing and coping with the ***fear of recurrence*** and ***depression***, and for coping with a "new normal" ***Coordination support*** for transition to fewer visits with oncology and more ongoing care with primary care physician ***Communicatio***n focused on late effects of anticancer treatment and advice and support for ***rehabilitative*** and ***self-management*** interventions to boost recovery Focus on ***health maintenance*** and cancer prevention, advise for ***lifestyle*** change (e.g., food, exercise, stress, and sleep) Screening for ***late effects*** and ***emerging morbidities*** of cancer therapy (a high priority) and tumor recurrence
Patients living with cancer	Treatment of ***complex symptom burden*** due to metastatic disease and ongoing cancer-directed therapies Treatment of ***depression, anxiety***, and ***spiritual and existential distress*** regarding terminal illness Ongoing visits with oncology and involvement of cancer ***palliative care team*** (established benefits) Communication focused on ***understanding of illness and prognosis*** **End-of-life planning**

The importance to focus on clinical care and survivorship research also on the needs of metastatic cancer survivors, as promoted by Park, Peppercorn, and Al-Jawahri 2018, was emphasized and further refined by two survivors, one being himself an oncologist [23]. They (Langbaum and Smith) compare key issues (physical, emotional, sexual, screening for recurrence and screening for preventable conditions, coexisting illnesses, potential for inheritance, caregiver, financial, and care coordination) faced by cancer survivors whose disease is cured or in remission with those key issues faced by survivors with metastatic cancer. Important differences include

- that metastatic survivors experience ongoing physical, emotional, financial, caregiver-related, and care coordination key issues (in contrast to cured survivors with typical decreasing burdens),
- guidelines are often lacking in metastatic survivors for key issues such as sexual issues or screening for preventable conditions (e.g., heart disease).

[3] Table from Park ER, Peppercorn J, El-Jawahri A. JNCCN 2018, adapted by FS

Interestingly, the authors also discuss not only needs but also among key issues the available guidelines and care models for cancer survivors. A key message is that guidelines and evidence for metastatic survivorship care are far less existent than for survivors in remission or cure.

However, the patient needs and clinical issues of **metastatic survivors** are largely overlapping with those described vastly in the literature (on patient needs [39] and symptom burden [40] as well as interventions) and guidelines [41] of **early integrated cancer palliative care** [21]. An important development is therefore to utilize the workforce of double-boarded palliative care and oncologist, who deliver *cancer* palliative care by integrating oncology-specific and palliative care-specific interventions, in metastatic survivorship care. The **ESMO designated centers of integrated oncology and palliative care** may serve as a role model for clinical care (65% of the centers had double-boarded palliative oncologists) and may engage more explicit in survivorship care [42]. ESMO does not provide specific survivorship guidelines, but guidelines on supportive and palliative care covering main topics relevant in survivorship care.

The definition of cancer survivorship in the **ESMO patient guide** [18] includes metastatic survivors but limits patients living with cancer to (Quote) "*people with well controlled disease and few symptoms, who receive treatment to manage cancer as a chronic disease.*" Also the acute phase (see above) is excluded in the definition, the definition states (Quote) "Survivorship focuses on health and the physical, psychological, social and economic issues affecting people after the end of the primary treatment for cancer."

ESMO and European Cancer Patient Coalition Categories of Cancer Survivors (Who Are all Post-Treatment)

- people having **no disease** after finishing treatment,
- people who **continue to receive treatment** to reduce the risk of cancer coming back,
- people with **well-controlled disease** and few symptoms, who receive treatment to manage cancer as a chronic disease.

Key issues, according to the ESMO and ECPC Patient guide, **in survivorship care** are issues related to **follow-up care**, the management of late **side effects** of treatment, the improvement of **quality of life,** and psychological and emotional health. Survivorship care includes also future anticancer treatment where applicable. Family members, friends, and **caregivers** should also be considered as part of the survivorship experience.

To round up the summary of definitions of a cancer survivor, a **systematic review of published definitions** [17] concludes that (Quote) "*there is not a unique definition of who is a "cancer survivor" and what is "cancer survivorship*"", but also that (Quote) "*the most widely used definition sees cancer survivorship as a process that begins at the moment of diagnosis and continues through the balance of life*."

In conclusion, the **definition of cancer survivorship** and **who is a survivor** shall strengthen the identity and belonging of the cancer patient, support compassionate and efficient communication, support holistic needs-based care, and foster tailored survivorship care program development.

Considering the medical landscape in many parts of the world with quite well established (a) acute care facilities with integrated support services such as psycho-oncology, social work, supportive care consultants, acute rehabilitation, and so on and (b) palliative care services run by multiprofessional teams and providing adequate expertise in oncology, a survivorship definition covering both (a) the acute phase and (b) the complex metastatic and close to end-of-life phase may overstretch the definition.

Therefore, **the joint ESMO and ECPC definition** of a survivor with (1) cured patients without anticancer treatment, (2) the patients undergoing adjuvant anticancer treatment in curative intent, and (3) patient with incurable but well-controlled tumor with or without anticancer treatment is a quite suitable definition. In these three situations, the **emphasis of care is needs-based** and **not driven by anticancer treatment topics or** by **complex medical and psychological complications** as typical for cancer palliative care. In other words, when the oncological situation is **stable** either in cure, or adjuvant/maintenance treatment, or well-controlled metastatic situation then the patient is challenged to deal with side effects and (long-term) toxicities of anticancer treatment, readaptation of life to new normality and meaning, go on a healing path to cure traumas and fears, and adapt to often only partially improvable disabilities (e.g., musculoskeletal, fatigue, CINP, lymphedema, stoma). To raise awareness of all these issues and provide professional and peer support, the ESMO-ECPC definition is indeed helpful and may guide oncology professionals to actively assess and listen to these patients and proxies.

Evidence-Based Survivorship Care Interventions

In survivorship care, several programs developed in the last decades, stimulated substantially by the IOM-report 2006.

Survivorship Care Plan

One key recommendation of the IOM-report was the implementation of an individualized survivorship care plan. Many institutions picked this up, also the ESMO-ECPC patient guide contains major elements of a survivorship plan (SCP). SCPs are documents given to the patient after a consultation with a health care professional, providing basic information on the cancer survivor's cancer diagnosis (stage, etc.), past or current anticancer treatments, follow-up visits to detect cancer recurrence, progression or second primary cancer, advice on secondary prevention of cancer and of (new) morbidities, information on potential late side effects of anticancer treatment. In addition to follow-up care and surveillance to detect recurrence,

progression, or secondary cancer, important topics (like content from the ESMO-ECPC patient guide) include (a) Support in coping with the new reality—Who can help me?, (b) Life after initial treatment—How can I get my normal life back?, (c) Preventive health—What lifestyle changes can I make to achieve optimal physical and emotional health, and (d) Detection and management of treatment—or tumor-related symptoms and comorbidities.

However, even though SCP in cancer is in many clinics standard-of-care, their effect is unclear. A recent meta-analysis and systematic review report that the SCPs are ineffective [31]. The authors included eight articles for the meta-analysis (n = 1286 survivors) and 50 for the systematic review (n = 18,949 survivors; n = 3739 health care professionals). The authors conclude as implications for practice (Quote): "*although SCPs appear to be feasible and may improve health care professionals' knowledge of late effects and survivorship care, there is no evidence that SCPs affect cancer survivors' patient-reported outcomes. In order to justify the ongoing implementation of SCPs, additional research should evaluate SCP implementation and the research design of comparative effectiveness studies. Discussion may also be needed regarding the possibility that SCPs are fundamentally ineffective.*"

Oncologist Versus Primary Care Provider

Whether primary care physicians can provide survivorship care remains controversial. Primary care is often involved in the management of cancer patients' needs, symptoms, and comorbidities, especially in the older population. The core values of primary care, coordination, and continuity of care, make primary care suitable to improve survivorship care. But the role of primary care may depend on the setting and the care context (e.g., gatekeeping models such as the UK). A systematic review analyzing 16 studies conclude that survivorship care by primary care is feasible, but needs education for GP's and advanced health care systems [43].

Models of Cancer Survivorship Health Care

Currently, several models are developed and promoted depending on the setting of care and the living situation of the survivor. Examples are the risk-stratified shared care model of cancer survivors (from a US academic cancer center), the United Kingdom National Health Service breast and lung cancer pathways, and a Community Solution for Cancer Survivorship Care [13]. A systematic review assessed 25 studies exploring different survivorship care models [44]. The authors conclude (Quote): "The reviewed survivorship model studies were comprehensive but were limited by a lack of existing rigorous evaluation efforts to assess their effectiveness." Important results of the review were (a) the awareness of the crucial role of care coordination which often required improvement and (b) the importance of obtaining data on the effectiveness of these survivorship models to ensure satisfactory quality of life and health outcomes.

These discussed models provide a few important points:

(a) **risk-assessment** of survivors for recurrence of cancer, debilitating (late) side effects (physical, emotional, social, vocational) and toxicities, and comorbidities,
(b) utilization of the **oncology cancer treatment pathway** methodology with pre-planned timepoints of follow-up, amended by survivor's needs screen,
(c) involvement of **primary care** and **community professional resources** in detecting debilitating long-term toxicities and comorbidities and promoting a healthy and secondary-preventive lifestyle in a motivating, social context. In the community cancer survivor support and/or peer-groups may become an important resource, can contribute to promote a new perspective and self-confidence, and also allow discussion of sensitive issues such as changes in relationships and in family, dealing with children and fertility, and sexual life. The community is also the "right" place to tackle issues around return-to-work and finances, finding new interests and hobbies suitable for the physical and psychological situation/disability as a cancer survivor, and engage in a healthy lifestyle with physical activity, nutrition and management of weight, stress, and dependence from nicotine or alcohol.
(d) Importance of structured and proactive **care coordination.**
(e) Agreement on key **outcomes** for evaluation of survivorship care models. Currently, the standardization of assessment methods, outcome classification, and severity grading of morbidity and symptoms of survivors are underdeveloped as the large variation in assessments and definitions show. A systematic review tackling childhood cancer survivors pleas for global collaboration [45].

Quality of Cancer Survivorship Care Framework

To contribute to new standards of quality of cancer survivorship care, suitable for clinical settings, research, and policy a group of federal employees and academics, partially liaised to the Office of Cancer Survivorship, National Cancer Institute, developed a framework [46]. The framework defines quality domains and proposes indicators for (a) issues pertaining to cancer and its treatment, (b) general health care including comorbidities and prevention, and (c) health care delivery.

Cancer and its Treatment

*Prevention and Surveillance for **Recurrence** and **New Cancers**.*

- Assessment of risk predisposition including family history
- Referral and receipt of recommended genetics evaluation
- Recommendation for adjuvant and/or risk-reducing strategies
- Assessment of adherence with recommended adjuvant and/or risk-reducing strategies
- Clinical surveillance visits recommended and completed per guidelines
- Laboratory surveillance testing recommended and completed per guidelines
- Imaging surveillance recommended and completed per guidelines

*Surveillance and Management of **Physical Effects.***

- Assessment of **symptoms** and/or **conditions** via history, physical examination, and/or standardized instruments, tailored by cancer type and treatment exposure:
  - Visual (e.g., cataracts, visual impairment, dry eyes).
  - Hearing (e.g., ototoxicity, tinnitus, hearing loss).
  - Oral/dental (e.g., loss of teeth, dry mouth, trismus).
  - Ear/nose/throat (e.g., dysphagia, sinusitis).
  - Endocrine (e.g., central endocrinopathies, hypothyroidism, hypogonadism, growth hormone deficiency, osteopenia, osteoporosis).
  - Cardiac (e.g., dyspnea, coronary artery disease, valvular disease, congestive heart failure).
  - Pulmonary (e.g., fibrosis, restrictive lung disease, shortness of breath, oxygen dependence, cough).
  - Gastrointestinal (e.g., diarrhea, proctitis, gastroesophageal reflux, bowel obstruction, bloating, eructation, hernia, small bowel obstruction).
  - Hepatic (e.g., hepatitis, fibrosis, cirrhosis, focal nodular hyperplasia).
  - Genitourinary (e.g., urinary toxicity, urinary incontinence, hematuria).
  - Immunological (e.g., asplenia, immunodeficiency, graft versus host disease).
  - Male genital (e.g., anorgasmia, azoospermia, dry ejaculate, penile shortening/curvature, retrograde ejaculation).
  - Gynecological (e.g., vaginal dryness, pain with intercourse, uterine insufficiency, vaginal stenosis, pelvic floor dysfunction).
  - Musculoskeletal (e.g., scoliosis, pain, post-mastectomy pain, post-thoracotomy pain, bone fractures).
  - Dermatological (e.g., dry skin, graft versus host disease manifestations, skin color changes, skin texture changes, loss of hair).
  - Neurological (e.g., neurotoxicity, peripheral neuropathy, imbalance, spasticity).
  - Neurocognitive (e.g., memory changes, behavioral changes, concentration).
  - Vasomotor (e.g., hot flashes, irritability).
  - Vascular (e.g., carotid stenosis, aneurysms, cerebrovascular accident, moyamoya).
  - Body composition (e.g., sarcopenia, cachexia).
  - Frailty.
  - Reduced exercise tolerance.
  - Overall burden of physical symptoms.
- Referral and **receipt of recommended evaluation** including, as indicated, laboratory, imaging, and/or specialty care
- Recommendation and **receipt of appropriate treatment**, such as medication, therapy, and/or exercise
- Recommendation for **risk-reducing strategies** (e.g., weight loss, exercise, pharmacological treatment)
- Assessment of **adherence** to recommended treatment and/or risk-reducing strategies
- **Reassessment** of symptoms and/or conditions at defined intervals and/or treatment phase

*Surveillance and Management of **Psychosocial Effects***

- Assessment of **symptoms** and/or **conditions** using history or validated instruments, general and tailored by cancer type and/or treatment exposure.
- **Psychological**
  - Fatigue.
  - Stress.
  - Post-traumatic stress.
  - Post-traumatic growth.
  - Distress.
  - Anxiety.
  - Fear of recurrences.
  - Sleep disturbance.
  - Coping.
  - Worry.
  - Illness intrusiveness.
  - Cognitive changes.
  - Educational problems.
  - Social withdrawal.
- **Financial and/or employment**
  - Financial toxicity.
  - Underemployment, unemployment, return-to-work.
  - Work productivity.
  - School productivity.
  - Insurance status.
- **Interpersonal**
  - Sexuality and/or intimacy.
  - Fertility.
  - Family and/or caregiver relationships.
- Recommended evaluation provided (e.g., laboratory testing, imaging, referral to specialty care)
- **Treatment p**rovided (e.g., medication, therapy, exercise)
- Assessment of **adherence** to treatment completed
- **Reassessment** of symptoms and/or conditions at defined intervals and/or treatment phase

General Health Care and Prevention

Surveillance and Management of Chronic Medical Conditions

- Evaluation and treatment of **noncancer medical conditions** (e.g., hypertension, diabetes, depression) using disease-specific indicators
- **Medication** reconciliation

Health Promotion and Disease Prevention

- **Prevention-focused visits** and testing (e.g., screening for diabetes, hypertension, hyperlipidemia)
- Age- and gender-appropriate **cancer screening** (e.g., Pap smear, mammogram, colonoscopy), recommendation, referral, and receipt of screening
- Assessment of **lifestyle** behaviors, referral, and treatment (e.g., smoking, alcohol, sun protection)
- Assessment of **weight** management (e.g., obesity, physical activity, diet), referral, and treatment
- **Vaccination** advise and assessment of vaccination rates (e.g., influenza, pneumonia, meningococcal, shingles, particularly among those who may be chronically immunocompromised)
- Screening for exposure to **infectious exposures** (e.g., HIV, hepatitis B, hepatitis C)

Health Care Delivery

Clinical Structure.

- Type of **health care delivery environment** (e.g., primary care office, oncology office, survivorship clinic, academic medical center/community-based hospital, urban/rural)
- Status of cancer survivorship **providers' education and/or training**
- Availability of needed **specialty care** (e.g., cardiology, nephrology, endocrinology)
- Availability of needed **health care professionals** (e.g., psychology, art, music therapy, nutrition, social work, physical therapy, sexual health)
- **Access to care** enabled (e.g., availability of appointments, financial counseling, navigators)
- Availability and functionality of **health information systems** (e.g., electronic medical records, telehealth)
- Opportunities for **research participation** offered

Communication/Decision-Making

- **Information/education** provided and understanding assessed while taking into account **health literacy** (e.g., survivorship care plan may serve as a tool, *but consider that the effect of SCP is still unsure*)
- Assessment of **self-management skills** and support and/or advice provided
- **Advance care planning** discussion and/or documentation
- Discussion of **sensitive topics** (e.g., sexual activity, continence, end-of-life care, children, literacy, racial issues)
- Cancer care team involves **family members** or friends in discussions

- Involvement in **shared decision-making** (e.g., assessment of risk perception, values, decision support)
- **Respectful communication** with patient
- Care consistent with **patients' goals of care**

Care Coordination

- Discussion with patient about **care planning, documentation, and sharing** with patient and care team (e.g., survivorship care plan as tool may be considered)
- Evidence of communication between **oncology specialists** and **primary care providers**
- Evidence of communication between **other health care professionals**, oncology team, and primary care providers
- Providers aware of important information about patient's **medical history** and/or ongoing care
- Patient and cancer care team office talked about all **prescription medications** the patient was taking

List adapted from Box 2; Nekhlyudov L, et al. *J Natl Cancer Inst 2019 Nov 1;111(11):1120–1130.*

COMMENTARY.

In summary, this list provides key quality indicators both for specific survivorship care and general health care, but also of "common good cancer care" (e.g., respectful communication, shared decision-making, good communication among providers).

Evidence Gaps and Research Priorities

A recent workshop, guided by NCI, provides information on current evidence gaps and research priorities [28].

Surveillance for Recurrence and New Cancers

– Identify optimal evidence-based **schedules for surveillance** of recurrence and new cancers.
– Generate better estimates of risk and potential benefits of surveillance testing.

Management of Long-Term and Late Physical Effects

– Incorporate, in a consistent manner across studies and existing data resources, **data collection** using common data elements for **symptoms, functional status**, and **comorbid conditions.**
– Examine the natural history and **biosignatures** of late and **long-term effects** by cancer type and treatment.
– Utilize theoretical models, such as the chronic disease model, to **frame intervention development** for preventing and mitigating long-term and late physical effects.

Management of Long-Term and Late Psychosocial Effects

- Conduct population-level surveillance for **psychosocial sequelae.**
- Examine psychosocial consequences of or contributors to living with advanced/metastatic disease, recurrence, second malignancies.
- Greater uptake of **screening for psychosocial risk** concomitant with cancer diagnosis, treatment, and/or follow-up care.
- Identify **social functioning** needs of **aging** long-term cancer survivors.

Health Promotion

- Conduct multilevel research studies addressing **health behaviors** in survivorship care in both oncology and primary care settings.
- Integrate existing and emerging digital technologies for **tailored health promotion** into survivorship care.
- Combine basic science with human studies to identify mechanisms and targets for interventions.

Care Coordination

- Define **key outcomes** and measures to assess care coordination.
- Develop algorithms for **risk-stratification** and implement **tailored care pathways** for survivors based on levels of needs.
- Evaluation of the role of **telehealth** in coordinating comprehensive survivorship care.

Financial Hardship

- In longitudinal studies, characterize **risk factors** for financial hardshipemployment disruption, and other economic effects of cancer and evaluate financial hardship outcomes such as on daily functioning, clinical outcomes, quality of life, and health care utilization.
- Leverage existing data sources and novel data linkages to study the economic effects of cancer.
- Develop technology to streamline the collection and use of **economic data** to support financial navigation interventions.
- Interventions to mitigate the economic effects of cancer should address issues at the patient, provider, health system, employer, and policy levels.

Cross-Cutting Needs

- Understand and address **disparities** by including understudied, underserved, and vulnerable populations in studies.
- Conduct longitudinal as well as longer term follow-up studies (>5 years).
- Incorporate implementation science expertise in interventions to **translate findings** from observational studies and efficacy trials **into practice.**
- Develop career development, **training and mentoring** programs, and other strategies to support cancer survivorship scientists.
- Leverage existing studies (both observational and interventional) for cancer survivorship research.

List adapted from Box1. 2019 National Cancer Institute Cancer Survivorship Workshop Research Priorities.

In summary, this list provides important insight into the myriad of open issues in survivorship care, including the plea to monitor more systematically survivor's needs and morbidities and develop and monitor effective interventions, taking advantage of the modern world (e.g., telehealth).

Conclusion

The definition of a cancer survivor seems to be most useful when people confronted with cancer after acute, intensive anticancer treatment and in the metastatic setting with well-controlled tumors are included. The reason for this is that the focus is on patient and proxies needs, dealing with disabilities, return to and define new with often new meaning the best possible life including health promotion. Currently, the evidence base for overall survivorship care is scarce, whereas for specific interventions to detect recurrence, promote healthy lifestyle, or management of specific functional deficits or symptoms sufficient or good evidence is available. Currently, the evidence to promote ubiquitous survivorship care plans (SCP) is not available, probably the SCP integrated into risk-adapted and community-based care may gain importance. The key to survivorship care is to be aware of the myriads of burdens cancer survivors are confronted with, the importance of listening as professional and proactively coordinate care.

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Goals of Survivorship Care

2

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Cancer Survivorship Care

Cancer survivor is defined as anyone with a diagnosis of cancer and who is still alive [1]. In recent years cancer survivorship has increased significantly and around 25% of people surviving after a cancer diagnosis have the same life expectancy as the general population. In Europe and in the United States, the number of individuals

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living after a cancer diagnosis (i.e., cancer prevalence) is growing by approximately 3% annually. They currently represent more than 5% of the overall population in high-income countries (i.e., at least 20 million in Europe and 17 million in the USA) [2–4].

A recent study has estimated population-based indicators of cancer cure in Europe by type, sex, age, and period [5]. The study used information from the EUROCARE-5 dataset, including 7.2 million cancer patients (42 population-based cancer registries in 17 European countries) diagnosed at ages 15–74 years in 1990–2007 and at least 18 years of follow-up. Cure fraction was defined as the proportion of cancer patients having the same mortality rates as those observed in the general population of the same sex and age.

The cure fraction of European cancer patients increased in the 10 years examined, in both sexes (Fig. 2.1) reaching 39% among men and 51% among women, for all cancer types combined, diagnosed in 2000 at all ages (15–74 years). The cure fraction was 94% in men, when the diagnosis was testicular cancer, 76% in men and 86% in women with skin melanoma, 70% in men and 87% in women with thyroid cancer, 67% in men and 75% in women with Hodgkin lymphomas. Cure fraction was also 76% for patients with cancers of corpus uteri, 66% for those with cancer of the breast, 64% for those with cancers of the cervix uteri, and 63% for those with cancers of the prostate. On the other hand, the proportion of cure was very low (below 15%) when the diagnosis was a cancer of the pancreas, liver, esophagus, lung, brain, chronic leukemia, and myelomas.

Notably, two-thirds of cancer patients, diagnosed at age 15–44 years (65% in men and 69% in women), were expected to be cured, while the proportion was approximately one-third for patients aged 65–74 years (33% in men and 38% in women).

Further studies explored other indicators of cancer cure [6, 7]. In particular, an Italian study [7] reported that, up to 2010, 27% of all prevalent cases (20% in men and 33% in women) could be considered as “already cured cancer patients” since their life expectancy (mortality rates) had become indistinguishable from that of the general population of the same age and sex. Assuming similar proportions for the European population, people living after a cancer diagnosis in 2020 who can be considered as already cured are at least five million, 1% of the overall population.

These results confirm the need to reconsider the current paradigm of survivorship as a never-ending experience. To recognize the increasing number of patients who will reach or have already reached a life expectancy similar to that of the general population provides an opportunity to improve quality of life by changing the way “former” patients view themselves, and it allows patients to return to their regular lives. The European Commission has recently acknowledged this need through the “Mission on Cancer” and “European Cancer Plan,” currently under approval. Currently, it is more important than ever to develop a concrete plan for the support of cancer patients after treatment. At the moment they will be considered free of disease (i.e., cured), we need to have a roadmap for future follow-up, if needed, and rehabilitation.

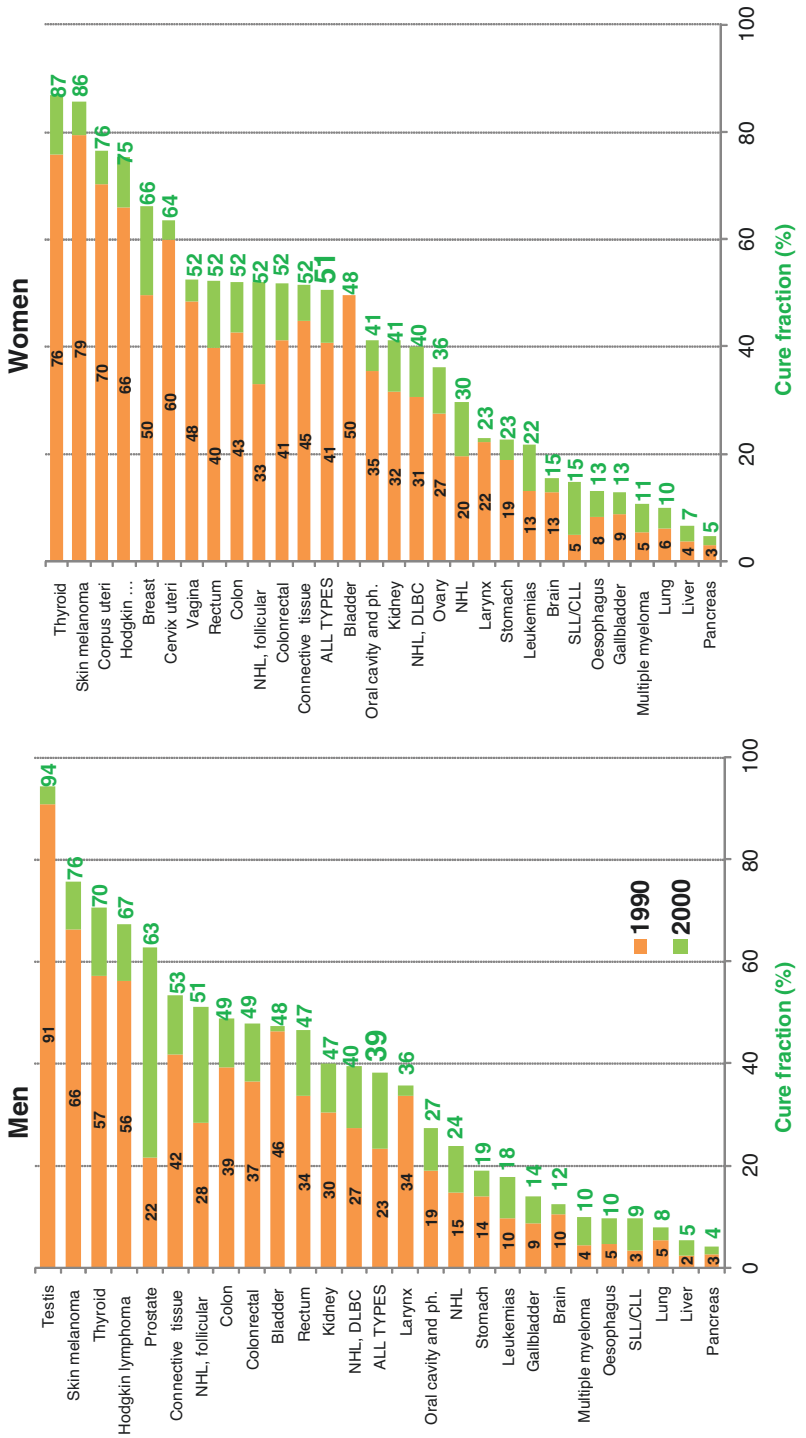

Fig. 2.1 Cure fraction after a cancer diagnosis in Europe, according to cancer type and year of diagnosis (adapted from [5])

Domains of Cancer Survivorship Care

According to the National Academy of Medicine report, titled "From Cancer Patient to Cancer Survivor: Lost in Translation" a cancer survivor's experience entails the entire range of the cancer pathway, i.e., diagnosis, treatment, remission, surveillance, after-cancer care, and end of life. As a definition and provision of care, survivorship pertains to the problems that are related to the capacity of a patient to obtain healthcare and follow-up treatment, late effects of treatment, second cancers, and quality of life. In the same report, it is highlighted that the essential goal of survivorship care is to shift cancer care from a model of illness to one of wellness.

For the delivery of survivorship care, the National Academy of Medicine defines four different components of healthcare provision to cancer survivors:

- Cancer surveillance and screening: In this level, surveillance is performed in order to identify possible recurrence of the primary malignancy and evaluate the likelihood of any second cancer.
- Late effects and side effects management: Regarding the late effects' management, there is ongoing research both for childhood and adult patient's types of cancer. The main aim of this research is to identify the potential late effects of cancer treatment and provide clinicians and caregivers with the tools to identify them promptly, and support more efficiently cancer survivors. The relevant body of research monitors the level of health maintenance and vital organs function that may be related to each treatment received.
- Risk reduction and cancer prevention: Regarding the risk reduction and prevention of future cancer occurrence, various behavioral interventions are suggested, in order to promote lifestyle changes, that have the possibility to reduce cancer incidence, but also several other illnesses, such as smoking cessation, healthy living, energy balance, and dietary changes.
- Psychosocial functioning: The psychosocial and economic consequences of surviving cancer treatments are equally important with the aforementioned, physical late effects. Cancer survivors and their families have to address many challenges, including economic burden, loss or interruption of social relationships, as well as emotional suffering that can last for a long time after a therapy is completed [8].

As someone can understand from the components, the healthcare support that is needed for cancer survivors requires the involvement of many different disciplines. Even more, depending on the age, cancer survivors may need support from even a more complex web of different healthcare services and practicians. Among elderly people, we can have the existence and interaction between multiple chronic conditions and different medications, occasionally the absence of social support, as well as particular goals of therapy (e.g., aggressive—and many times more effective—types of therapies are not suitable for this cohort of cancer survivors). Survivorship care needs to be a healthcare service that will continuously evolve to adapt to older adults' health needs.

According to the summary of evidence by Halpern et al., there are various models describing the delivery of such survivorship care [9]. These different models of survivorship care can be disease-specific or general, dependent on different types of cancer care professionals, as well as focusing on the care provided in separate survivorship clinics where cancer treatment was received or focusing on integrating survivorship care into a broader oncology practice.

Depending on whom among the clinicians (e.g., oncologists, primary care providers (PCP), or a combination of both) is managing survivorship care, a cancer survivor may get different types and intensity of care. Primary care providers and cancer specialists may have different priorities and scope on how they deliver cancer survivorship care; they may also have differing knowledge and clinical skills. In a similar fashion, cancer survivors may have different views about the importance of their various healthcare providers. In this manner, the models of survivorship that have been proposed were primary care-based (e.g., a primary care provider manages the survivorship care), specialty care-based (e.g., an oncologist takes ownership of survivorship care), and shared care models (e.g., joint management and responsibility of survivorship care).

Among these, the shared care model has been suggested to be the best way to optimize care for cancer survivors and guarantee high-quality care. Shared care allows for flexibility in providers' roles and responsibilities over time. It can also be flexible and efficient to the different needs of cancer survivors, which are dependent on time since diagnosis and completion of treatment, as well as recurrence status, and presence of other chronic conditions. It is noteworthy to mention, that a successful shared care model needs a tailored integration of primary care and specialty multidisciplinary healthcare providers with expertise in oncology, as well as in geriatric care for older cancer patients. The follow-up of cured and disease-free cancer patients will be at best delivered within cancer centers or oncological hospitals but separately from the oncology department to avoid that the specialized human resources are diverted from treating cancer patients in the acute phase of treatment. A crucial element of the shared care model is the need to have an established, interactive communication channel (e.g., with the use of well-designed e-health interventions) between primary care and specialty care providers. Many diseases such as nutritional and metabolic problems are common for cancer patients. Many oncologists seem to focus just on the disease (cancer) treatment while neglecting other health issues [10].

Finally, another model of cancer survivorship care delivery is risk-stratified care. In this model, the frequency of encounters with cancer specialists is directly related to patients' clinical needs, including the risk of recurrence and their late effects. For example, an older woman diagnosed with early-stage breast cancer treated with excision alone might not need to see a medical oncologist for ongoing care. Instead, she could transition to being managed exclusively by her PCP unless she experiences a recurrence for which she will receive specialty care. Integration of both psychosocial and somatic rehabilitation for cancer survivorship is clearly proposed under the fourth pillar of the Europe Beating Cancer Plan. Provision of patient-centered services from a multidisciplinary team and focusing on education, increase

of patient involvement in research, and dissemination of information should be at the core of survivorship care strategy. The active involvement of patients in their care is critical to better understand their needs, wishes, and preferences.

Cancer Survivorship Care Plan and Rehabilitation Targets

Cancer Survivorship Care Plan

In Recommendation 7, the Mission on Cancer calls for an "EU-wide research programme and policy support to improve the quality of life of cancer patients and survivors, family members and careers, and all persons with an increased risk of cancer" [11].

Such a program should aim to:

- develop a methodology to assess the health-related quality of life;
- develop tools to enable patient involvement in decision making;
- establish comprehensive programs at the international level based on patient-reported outcomes to monitor the physical and psychosocial needs of cancer survivors (e.g., return to work, fertility, sexuality, reconstruction surgery, dental health, cognitive functioning, fear of recurrence, etc.);
- support research to close the knowledge gaps regarding the negative consequence that a cancer diagnosis or treatment has on a patient's physical, mental, and social health, both in the short and long term;
- develop long-term follow-up programs to better understand the needs and challenges of pediatric and young cancer patients;
- initiate research to assess the discrepancies and discrimination that cancer survivors face in different countries, including their access to legal and financial services (e.g., loans, mortgages, life insurance);
- support research into prediction models for the side effects of cancer therapies;
- assess the efficacy of the survivorship care programs initiated by different heath systems;
- develop research to assess both the direct and indirect economic consequences that cancer survivors and their relatives have to cope with [12].

Cancer survivors are a vulnerable population that requires medical and nonmedical interventions and is particularly at risk not only of having a low quality of life due to the long-term side effects of treatment with consequences for patients' physical, mental, and social health but also, as the majority of cancer survivors are above 65 years of age, they are at risk of developing another cancer. Other factors that influence the quality of life of cancer survivors are the cancer-related comorbidities, reaction to stress, stigmatization, the survivor's socioeconomic status, and access to quality healthcare and rehabilitation services [13].

For many people it is very difficult to remember all the details of cancer treatment, to record the needs that are rising during the treatment, and afterward to have

steadily on mind the plan of the follow-up care [14]. This need of survivorship care can be fulfilled with the existence of a structured and detailed survivorship care plan. Keeping a personal healthcare record can be useful and facilitate all the process.

Using this tool in survivorship care can facilitate the everyday life of cancer survivors and can reduce the pressure and the amount of work from the healthcare professionals.

Survivorship care plan should be individualized to the needs of each patient. The survivorship care plan should be customized to the needs of each cancer survivor, and should include basic information about the cancer type, the type of therapy received (biologic therapy, chemotherapy, surgery, radiotherapy, etc.), the possible side effects experienced from the therapy/ies and the other needs that possibly can arise during the period of therapy and afterward.

Furthermore, the essential role of survivorship care plan can be highlighted through the fact that survivorship care plan can be a useful tool for the oncology team of each cancer survivor as for the other healthcare professionals that are related with the cancer survivors. Healthcare professionals can use the survivorship care plan in order to carry out a structured and detailed follow-up [14].

Summary of cancer treatment consists of details about the personal medical history of the patient, the family medical history and a possible genetic counseling, information about the time of diagnosis, and the kind and sequence of treatment/s. The main contributors to the cancer treatment are basically the oncology team (medical oncologist, radiation oncologist, surgeon, nurses).

The after-treatment care plan includes the follow-up care plan (when should patient perform the suitable follow-up exams like computer tomography or laboratory exams, or other tests) and taking advice from your care team about tasks of the everyday life like sleep, exercise, sunscreen, immunizations, healthy weight programs, and helping to quit with smoking. Moreover, in the after-care plan are included other issues like providing psychosocial support to those who need it, financial planning, money and job problems, and problems in the relationship with friends and family. All the abovementioned parts of survivorship care plan are aspects of everyday life, that strongly concern most of the cancer survivors and that probably seek to be resolved [14–22].

Rehabilitation Targets

Cancer and its treatment produce a multidimensional impact on patients' lives, affecting the physical, sensorial, cognitive, psychological, family, social, and spiritual functional level of each individual cancer survivor. The problems that can arise through this situation can affect the daily activities or the procedure of returning back to work or even have a long-lasting effect on the health of cancer survivors. Cancer rehabilitation is one of the most important milestones in cancer survivorship care. It can help cancer survivors cope in a comfortable way with the problems that can arise during and after the cancer treatment or problems that can arise through

the disease itself and it can help cancer survivors in optimizing the quality of life and recovering the normalcy of their lives.

Rehabilitation programs can be organized as separate outpatient programs delivered by a multidisciplinary team of healthcare professionals within cancer centers or oncological hospitals or can be delivered by specialized clinics. The goal of such rehabilitation programs is mainly to help as many people as possible to recover from the physical or psychological problems, that can be caused during the cancer trajectory and through the phase of the main treatment and support patients to become as productive and independent as possible.

Rehabilitation is useful not only for the patient's life but also for their families. Provision of psychological support for the entire family and the patient is a crucial aspect in survivorship. Such support can contribute to better management of different emotions and can improve quality of life. To achieve this, accredited infrastructures should be built, with geographical distribution, such as the Comprehensive Cancer Centers (CCCs) [1]. The 34 CCCs that currently are in operation in Europe cannot cope with the present demand for cancer care, and, therefore, measures should be taken to ensure that such centers will be established in all countries, while in bigger countries there should be one CCC per five million inhabitants. Structuring the collaboration between accredited CCCs will support innovation and cover the entire cancer research continuum for both cancer care and early detection methods. This impacts early translational research, clinical trials, outcomes research, and health economics [1].

- As a milestone of cancer survivorship care cancer rehabilitation has multidimensional targets, which consist of many aspects of the everyday life of cancer survivors such as:
- Overcoming as soon as possible the side effects that can be caused through the cancer treatment or learning to manage possible side effects and coping with them.
- Improving physical and psychological conditions in order to offset any limitations caused through the cancer trajectory.
- Getting back a good physical condition in order to return to everyday life.
- Improving or even regaining self-confidence and self-awareness.
- Learning to manage and whenever it is possible to overcome mobility problems (getting out of a chair, walking, getting dressed, etc.) or cognitive problems (difficulty thinking clearly, memory problems, etc.).
- Becoming more independent and less reliant on physicians and reducing the number of hospitalizations.
- Learning how to adopt healthy everyday habits like exercise, balanced and healthy diet, and preserving or achieving a healthy weight.
- Getting advices and ideas on how to cope with problems like family issues, problems in the relationship with friends, partner, or kids.

The goal of cancer rehabilitation at the end of the day is to help cancer survivors stay as active as possible in order to go back to work and to regain the most if not

every aspect of the everyday life before cancer, to improve the quality of life, to reduce the possible side effects and symptoms of cancer or its treatment, and to help the cancer survivors to be more independent and confident. Toward this direction establishment of survivorship cancer clinics could help significantly. These clinics should include a multidisciplinary staff that can provide person-centered services. This is of paramount significance because patients after the acute care are usually left. These centers except those that can be used for further survivorship research can also help in provision of psychosocial interventions and rehabilitation. Additionally, patient empowerment can take place in these comprehensive clinics [13].

Despite the high number of cancer patients who survive, most of the EU countries have a lack of integrated rehabilitation policies. On the one hand, we have the lack of knowledge and experiences of healthcare personnel on cancer patient rehabilitation while on the other hand research data lacks on late effects of cancer and its treatment [14–23].

The Different Needs for Survivorship Care

Cancer survivors range from cured people, free of disease 5 or 10 years after completion of treatment, to people who continue to receive treatment to reduce the risk of recurrence, and people with well-controlled disease and few symptoms, who receive treatment to manage cancer as a chronic disease. Cancer survivors can be people from all age groups including kids, adolescents and young adults, adult, and elderly people.

Survivorship care covers issues related to follow-up care, to the management of late side effects of treatment, to the improvement of quality of life, psychological, and emotional health. Survivorship care includes also future anticancer treatment where applicable. Family members, friends, and caregivers should also be considered as part of the survivorship experience.

Following the policy recommendations on cancer survivorship of the EU Joint Action on Cancer Control [20, 23], the European Cancer Patient Coalition-ECPC has collaborated with the European Society of Medical Oncology-ESMO in developing the Patient Guide on Survivorship. The Guide offers to patients and their familys information in coping with the new reality of survivorship, on preventive health, follow-up care and most importantly, it includes the Survivorship checklist, care plan, and treatment summary that each oncology specialty clinician should fill in at the completion of each acute treatment modality for cancer patients free of disease (Fig. 2.2).

The collaboration of ECPC with ESMO was also extended to the clinical guidelines thus new and revised guidelines include also survivorship information that helps oncologists understand that cancer care after acute treatment enters a new phase: survivorship with its own requirements for care and follow-up.

Different key factors can explain the heterogeneity of needs among cancer survivors. The time of the survivorship caregiving, the type and stage of cancer, and the

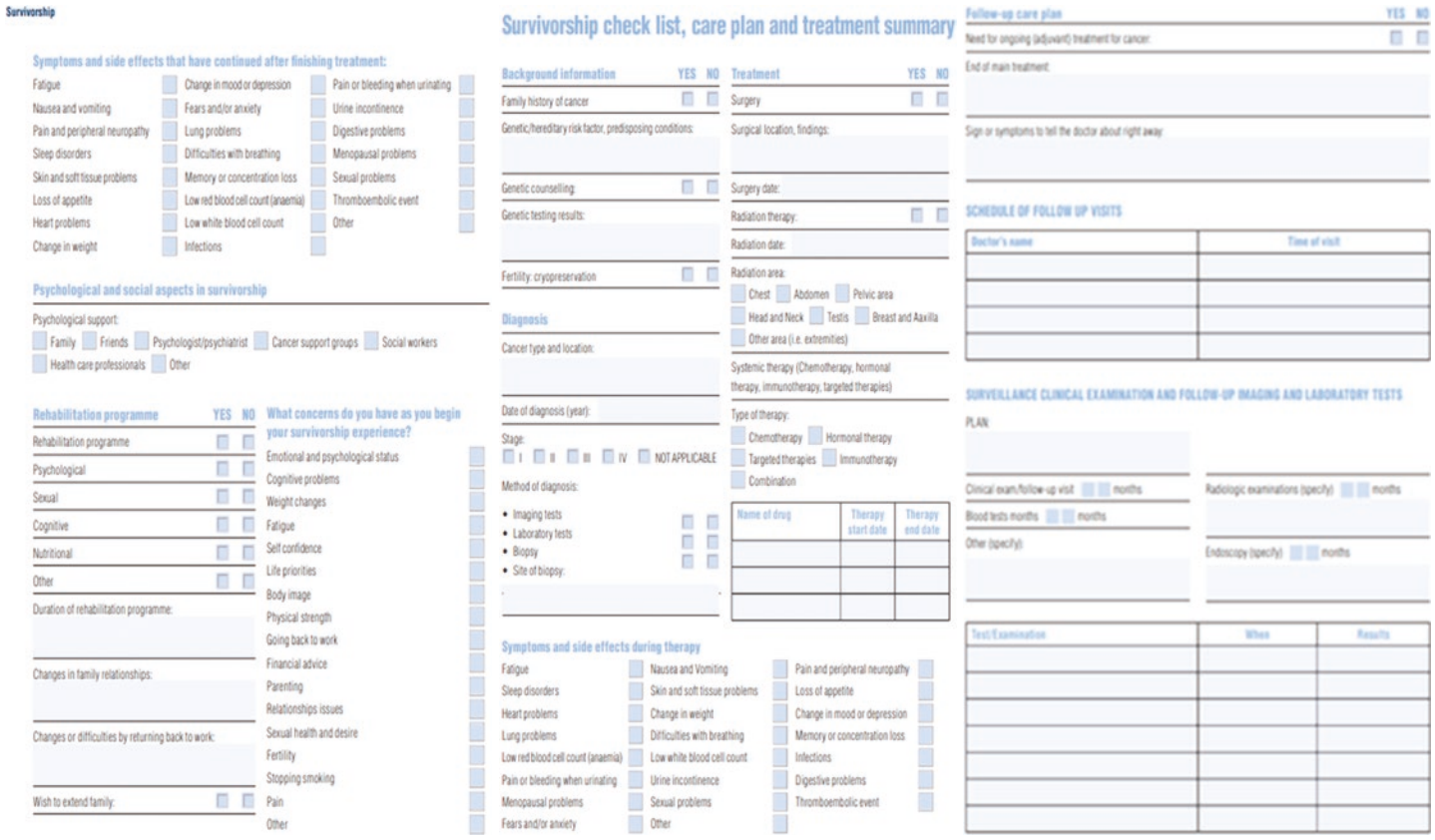

Fig. 2.2 Survivorship checklist, care plan, and treatment summary from the ESMO Survivorship Patient Guide (© ESMO)

status of treatment and in many cases the different age between cancer survivors are some of these factors. Furthermore, in the needs of survivorship care should be included the needs of family caregivers.

The role of a supportive network around the cancer patient cannot be emphasized enough: family, friends, colleagues, and community can play a significant role in managing emotional problems and assist patients to return to normal life. Some patients find it easier to discuss their concerns with people who experienced same cancer. A critical issue for this is patient empowerment which should be a role of healthcare professionals.

The type and stage of cancer and the consequent therapeutic procedures can significantly affect the type of needs, that a cancer survivor can have. Patients at the end of acute care treatment worry about the possible current or future side effects of their treatments. Furthermore, they possibly worry about the return to their normal habits and normal life.

People who completed their treatment and are considered cured after 5 or 10 years from the end of their treatment have different concerns and needs, like maintaining a healthy lifestyle, making their regular annual screening, returning to work, assuring their financial sustainability, regaining control of their life. People, who cope with cancer as a chronic disease, have different worries and different priorities focused on keeping the disease under control, maintaining the quality of life, and assuring the possibility to work [14].

Among cancer survivors, there are different views concerning essential needs of survivorship care. Some consider physical rehabilitation and regaining of the physical strength that they may have had before the cancer diagnosis, as the goals of the survivorship care. Others consider essential the psychological aspects of their lives that were affected by cancer and seek solutions through survivorship care. Others may have employment or financial issues as their main priority and as a result, their needs in the survivorship period will be heavily affected.

Cancer incidence is higher in the population around +65 years; however, cancer affects also children, adolescents, and young adults. Cancer is experienced differently by patients in different age groups which, consequently, have different needs during cancer survivorship.

Children and their parents may have worries about how cancer can affect their relationship with brothers, sisters, and friends. Young adults most often may have concerns about sexual life, relationship status, their education and job finding, as well as fear of recurrence.

Family caregivers are also a crucial part of the cancer pathway and of the survivorship experience and their needs are most often overlooked. Caregivers' needs differ depending on their age, employment status, their own health condition, and depending on whether the patient is in the acute phase of treatment or in survivorship status. Former caregivers (caregivers of patients who are in remission) could have different needs from current caregivers or bereaved caregivers. Former caregivers' basic needs consist of issues like managing interpersonal relationships or reintegration to family and social life and work. Current caregivers could have as main concerns issues like meeting patients' complex demands, maintaining

intimacy with partners, balancing own and patient's needs, and making decisions in the context of uncertainty. On the other hand, bereaved family caregivers have different needs like managing psychological distress and managing the loss of the patient, often struggling with financial issues that the disease has generated. Research into survivorship issues that will examine the variety of needs that can arise during the survivorship period will contribute to improving survivorship care [1, 24–29].

The Impact of National Disparities on Survivorship Care

Disparities in access to survivorship care are evident and are based on gender, age, ethnicity, geographical location, health status, etc. [30–32]. Different strategies exist for merging these disparities and they have been presented in official documents [33, 34]. Among European countries, different inequalities (between and within countries) exist in early detection, diagnosis, management, treatment, rehabilitation, adequate information, and bureaucratic issues that cancer patients have to deal with [34]. These inequalities are reflected in cancer outcomes, with the underprivileged having worse health outcomes due to worse access to healthcare services during and after the disease.

During the last decades, significant improvements have been achieved in health technology, which have impacted significantly in health outcomes. However, the rate of cancer incidence increases annually. Around 20% and 16.7% of male and female world population respectively will develop cancer in their lifespan and 12.5% and 9% of them will die of cancer [35].

Cancer inequalities, as highlighted in "Challenging the Europe of Disparities in Cancer-A Framework for Improved Survival and Better Quality of Life for European Cancer Patients" [35, 36] divide Europe from East to West and from North to South. Such disparities must be addressed to ensure that the provisions of the EU Beating Cancer Plan can be met and that they can benefit all European citizens.

Western and Northern countries are doing much better than the Southern and Eastern countries [37]. The Western and Northern European countries have better healthcare systems and provide better access to early detection programs and services and try to decrease the financial impact of the disease [38]. In Bulgaria for instance, only 6% of cancer diagnosis was the result of screening programs while the 94% was the result of a medical appointment for another health problem [39]. These disparities exist not only at the screening or diagnosis level but also with cancer treatment. After being disease-free, patients lack sufficient rehabilitation, psychosocial support services, and continuity of care. Cancer survivors report lower health status than before cancer experience, less health information, as well as that their family members do not look for information on cancer and that their income is low [40]. Inequalities in cancer are also illustrated by the fact that survival rates are also much lower in the Southern and Eastern European countries compared to the Northern and Western ones.

Survivorship research is of paramount importance to address the gaps and inequalities in survivorship care. As A. Berns et al. (2020) mention, we need first of all the appropriate infrastructure to translate research into actions. Many times, research just remains in published papers and is not implemented to respond to the needs of people. Involvement of different actors (stakeholders, policymakers, patient coalitions, etc.) in research is a key component of implementation. Implementation of clinical and prevention trials that would include also health economics, therapeutic interventions, and tertiary prevention measures should be a high priority of both researchers and policymakers.

In order to eliminate inequalities, different actions have been undertaken by CDC [41], while the EU Joint Action on Cancer Control (CanCon) has made clear recommendations in this area [42]. Some of the key recommendations proposed by the Joint Action on Cancer Control (CanCon)are [42]:

1. Embed equity within the cancer prevention and control policies in all European Union Member States.
2. Align cancer prevention and control policies with a Health in all Policies approach.
3. Adopt a Health Equity Impact Assessment framework.
4. Engage and empower communities and patients in cancer prevention and control activities.
5. Support the development of European research programs that help deliver equity in cancer prevention and control in all European Union Member States.
6. Improve equitable access and compliance with cancer screening programs.
7. Ensure equitable access to timely, high-quality, and multidisciplinary cancer care.
8. Ensure equitable access to high-quality surgical care in all European Union Member States.
9. Ensure that all patients have timely access to appropriate systemic therapy.
10. Develop national cancer rehabilitation and survivorship policies, underpinned by an equity perspective.

The Cancer Stigma and Cancer Advocacy

Despite the improvements in diagnosis, treatment, technology, and life expectancy, cancer continues to be seen as a stigmatizing disease. Stigma relates to cancer as a life-threatening condition [43–45]. Thinking about the disease can remind patients about their feelings at the time of diagnosis and treatment, such as fear, stress, depression, awkwardness, self-criticism, shame, guilt, and low self-esteem. [46, 47]. These feelings emerge because of still prevailing beliefs that a cancer diagnosis is a death sentence [48]. However, stigma does not affect only cancer patients themselves, but it also permeates into and impacts society.

The Joint Action on Cancer Control (CanCon) has paved the way toward reducing the cancer burden within the European Union by proposing policy

recommendations aimed at improving the delivery of cancer care and the quality of life of cancer patients and survivors. The policy recommendations coupled with the policy papers that accompany the main deliverable can support EU member states to prioritize cancer on their health agendas and to plan and implement high-quality rehabilitation and survivorship care for their citizens [49].

The focus points proposed by the Joint Action on Cancer Control cover the following aspects:

1. The need for a personalized follow-up program for each cancer survivor that includes the management of late effects and foresees the patient's needs for tertiary prevention; such programs should be implemented with the active involvement of survivors and their relatives.
2. The need to rethink the early detection of patients' needs and to improve their access to rehabilitation, psychosocial, and palliative care services.
3. The need for an integrated and multidisciplinary care framework that would enable the implementation of a survivorship care plan that can enhance patient empowerment and quality of life.
4. The need to foresee and address the late effects of cancer and its associated treatments pose to children, adolescents, and young adult survivors.
5. The need for enhanced research in survivorship in order to provide data on late effects and to assess the impact and cost-effectiveness of supportive care, rehabilitation, palliative, and psychosocial care interventions [50].

On the other hand, survivorship features high on both current European Commission emblematic initiatives: the European Cancer Plan and the Cancer Mission in Horizon Europe. The EU Cancer Plan was published in February 2021 and aims to deal with the whole disease pathway. The policy document focuses on four core areas, on which the European Commission will concentrate its efforts: prevention, early detection, diagnosis, cancer treatment and quality of life. The EU Cancer Plan aims to foster European collaboration and support EU member states to strengthen their national cancer plans as well as to be better prepared for future challenges. The EU Cancer Plan focuses more on new approaches to cancer with a specific focus on new technologies, research, and innovation, in order to provide better patient-centered services [51]. Patient-centeredness is also closely connected with the "Cancer Mission", the new research and innovation program in health, included in Horizon Europe [52].

To impact society at large, the Mission on Cancer aims at bringing countries together to achieve a significant reduction of the enormous EU cancer burden and improve the quality of life of patients by promoting cost-effective, evidence-based best practices in cancer prevention, treatment, and care [1]. The main goal for the implementation of a mission-oriented approach to cancer in Horizon Europe was to achieve a 10-year cancer-specific survival for three-quarters of the adult patients diagnosed in the year 2030 in the Member States with a well-developed healthcare system [1, 12]. However, achieving this goal poses significant medical, socioeconomic, legal, and political challenges.

Positioned as the last component of the cancer research continuum and an integral part of translational research, survivorship research can influence the assessment of multiple patient outcomes, including the health-related quality of life and the socioeconomic factors impacting survivorship. Any data collection from cancer survivors may be useful to detect and reduce long-term side effects of treatment, as well as to improve rehabilitation and psychosocial services [49].

The development of pertinent strategies, aiming to address the long-term effects of cancer treatment and to improve the health-related quality of life of cancer patients, should pay particular attention to the gaps between research and cancer care and prevention that can be found in areas such as psychosocial oncology, supportive care, rehabilitation, palliative care, and survivorship. Outcomes research is key for both therapeutic interventions and the effectiveness of public health services and interventions. A high-quality cancer care requires multidisciplinary expertise and adequate resources, together with high-quality data. Furthermore, due to the expansion of new evidence for diagnostics and therapy, innovation is essential and should be tailored to the individual needs of patients. Integrating cancer care and prevention with research and education will boost innovation and deliver a comprehensive multidisciplinary cancer care framework [1, 11, 12, 35, 36, 46–55].

Concluding Remarks

Europe counts currently 20 million cancer survivors and cured patients who, in most EU member states, do not receive any rehabilitation and survivorship care. The EU Cancer Plan sets an ambitious goal to be reached by 2030: a 10-year survival of 75% for cancer patients and living well after cancer.

Improvement of research and decrease of health inequalities in cancer care by improving cancer screening, early detection, equal access to treatment, and follow-up care are key strategies for European countries to reach the above goal. Provision of patient-centered services that focus on research, empowerment, education, and multidisciplinary care delivery should be the standard cancer care approach. Synergies among patients, researchers, civil society, stakeholders, and policymakers can help in establishing the patient-centric approach in the years to come, which is our key recommendation, which is also the core of the EU Cancer Plan.

Despite the high incidence of cancer, and abundant literature on health-related quality of life, patient-centricity, patient involvement in their care, there is a lack of concrete policies to ensure rehabilitation and lifelong survivorship care. Establishment of survivorship clinics in cancer centers, where multidisciplinary teams provide services can help in better rehabilitation and reintegration in social life and work. The multidisciplinary teams of these clinics can empower patients and provide tertiary prevention. Adaptation of patients to a healthier lifestyle can improve survivorship and health-related quality of life. Provision of detailed information and self-management education will decrease stress and make patients feel more confident and relying more on information from their medical team rather than from various Internet sources. The cancer survivorship care plan offering

information about the patient's diagnosis, treatment, and follow-up care [14] should become integrated into the discharge instructions of cancer patients across Europe. It will help any healthcare provider whom the cancer survivor will consult to have a clear picture of the patient's prior cancer experience, adverse events, and follow-up care. Digital health can play an important role, particularly in cancer supportive care settings, aiming to offer to cancer patients and survivors tools and assistance to cope with cancer care issues, and at the same time, improving the efficiency of the health-care system and liberating health professionals time for taking care of patients in the acute phase [1, 2, 7]. Survivorship research and care will become increasingly important in the following years, as a result of the increasing numbers of "cured" patients and cancer survivors.

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3 "There is Life after Cancer": The Medical, Psychological, Social and Financial Challenges of Cancer Survivors at the End of the Active Treatment

Grazia Scocca and Françoise Meunier

Introduction

The proportion of cancer survivors is increasing by 3% every year and in 2018 more than 12 million cancer survivors have been estimated in Europe.

Furthermore, in 2040, data predict an increasing number of oncological diseases will affect the European population, with +36% of diagnosis prior to the age of 69.

These data highlight the concerns about cancer diseases as an issue to tackle across the domains of medical science, policymakers, legislators, and the private sector.

In the last decades, important progress has been accomplished to strengthen prevention and ensure early detection as well as more effective therapies. Along with increasing knowledge about cancer disease, these developments remarkably improved cancer survival in the last years. To date, about half of patients who are diagnosed with cancer will survive for 10 years or more [1, 2].

The increase in the prevalence of cancer calls for the need for continuous monitoring of prevalence indicators to properly plan and allocate resources to cancer care, aiming to improve the quality of life of cancer survivors.

Whether being cured (disease-free) or not, cancer survivors do experience late and long-term effects of treatment, emotional distress, and fear of tumor recurrence. These effects represent challenges for health care systems, which have to ensure appropriate follow-up care and to promote optimal quality of life: moving from "how long" patient live after diagnosis to "how well" survivor can expect to live from diagnosis onward [3].

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For this purpose, the contribution wants to promote an investigation on the main issues concerning the medical, psychological, social, and financial aspects of life after cancer. The analysis aims to highlight the needs in terms of research along with the political and legal measures to implement, necessary to improve the quality of life and social rehabilitation of cancer survivors in the European area.

The structure of the article includes a preliminary focus on the notions of the quality of life and rehabilitation, and which will be at the basis of the argumentation to tackle the main challenges to promote the rights of cancer survivors.

The analysis will move then to analyze the issues linked to the late effects of the treatments, the psychological aspects, and the impact of socioeconomic life of cancer survivors.

Life after Cancer and the Notion of the Quality of Life

Cancer prevalence rates are still increasing in the European Union, leading to a growing population of people living with or beyond cancer. The concept of survivorship goes beyond patients who are fully cured and encompasses various situations patients have to face after the completion of the active treatment period. This may include former patients in remission or fully cured and who would need to return to normal activity; along with patients with recurrence after a prolonged period of remission who may receive new courses of treatment with curative intent. Survivorship also includes patients who live with incurable cancer as a "chronic disease" and receive life-prolonging treatment or palliative care.

Whether being cured (disease-free) or not, cancer survivors do experience late and long-term effects of treatment, emotional distress, and fear of tumor recurrence.

Therefore, the challenges for health care policy and cancer survivorship planning need to incorporate both the objective of "how long" a patient lives after diagnosis as well as "how well" the patient can expect to live from diagnosis onward. Consequently, the focus is progressively shifting toward the expectations for the quality of survival both after curative treatment and while living with recurrent disease.

The Council of the European Union invited the Member States to "take into account the psycho-social needs of patients and improve the quality of life for cancer patients through support, rehabilitation, and palliative care" [4].

The World Health Organization (WHO) defines the quality of life as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns. It is a broad-ranging concept, incorporating in a complex way individuals' physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationships to salient features of their environment" [5].

Quality of life is a multidimensional construct, individual-centered because the individual must evaluate his or her functioning across several domains [6]. According to the definition provided, quality of life encompasses physical functioning, emotional functioning, social functioning, role functioning, and overall

quality of life. Against this background, physical functioning refers to the impact of physical health on daily activities such as self-care and ambulation. Emotional functioning describes depression and anxiety. In cancer-related measures, this also includes fears about illness and recurrence. Social functioning refers to the ability to engage in meaningful social interactions, activities, and relationships. Role functioning indicates the degree to which individuals can carry out their usual roles at home, school, work, and in the community. Finally, the overall quality of life refers to individuals' global assessment of functioning in all domains of life [6].

In the aim to assess late effects and health-related quality of life (HRQL) of cancer survivors, the European Organisation for Research and Treatment of Cancer (EORTC) having a long tradition of Quality of life research has developed a cancer survivorship assessment strategy. It consists of a survivorship core questionnaire that can be used as a stand-alone questionnaire or in combination with a cancer site-specific (survivorship) module [7]. The project is also the most recent study collecting data about the quality of life of cancer survivors.

The study identified 116 generic survivorship issues, and on average, 26 site-specific survivorship issues per tumor site. It confirms as relevant issues for cancer survivors experienced the feelings of uncertainty about the future, fears related to recurrence of cancer, fears and worries concerning family members, feelings of depression and anger, feelings that others do not understand the impact of cancer, positive impact on social relationships, positive changes in (perception of) life, negative body image, cognitive problems, fatigue, sleeping problems, pain, sexual problems, and dealing with the chronic physical consequences of cancer. Over 30% of the issues were related to physical functioning, including chronic physical effects of cancer and its treatment, like Raynaud symptoms, neuropathy, joint pain, and muscle cramps. These issues receive relatively little attention [7].

Against this background, cancer rehabilitation plays a crucial role. Dietz has classified cancer rehabilitation according to cancer patients' physical and individual needs into four categories: preventive, restorative, supportive, and palliative [8]. Based on these categories, the effectiveness of rehabilitation has been reported for each stage of cancer treatment. In view of these situations, Dietz has pointed out that it will be necessary to focus on a concept of care that asks, "What is the best support that can be provided to enable cancer patients to readapt to society" [9]. On the other side, DeLisa has stated that "now that cancer patients" survival rate has increased, attention should be turned to maintaining cancer patients "QOL and prolonging it" [10]. In other words, a shift to an approach that aims to maintain the QOL of patients at a high level and not just improve their function and prognosis has become necessary. More recently, Silver et al. defined cancer rehabilitation as "medical care that should be integrated throughout the oncology care continuum and delivered by trained rehabilitation professionals who have it within their scope of practice to diagnose and treat patients' physical, psychological and cognitive impairments in an effort to maintain or restore function, reduce symptom burden, maximize independence and improve quality of life in this medically complex population" [11].

Dealing with survivorship and rehabilitation service requirements is a relatively new notion in cancer policy and several countries are still grappling with the issues of starting to develop policy and strategy stances of how to respond to these "new" demands. Emerging knowledge and demonstrated good practice are recommending several strategies to help address the complex issues associated with cancer survivorship [3].

Improving the Medical Dimension of Survivorship Care

As already mentioned, the end of cancer treatment does not signal the end of cancer care. In the survivorship phase, all aspects of the individual's well-being must be considered, including long-term physical effects of treatment, together with psychological, social, and economic needs.

Focusing on the first ones, in particular, cancer survivors have multiple medical conditions, often related to the late and long-term effects of their initial cancer treatment as well as conditions related to premature aging (e.g., fatigue, cognitive changes, decreased physical functioning) [12]. More specifically, the physical after-effects of cancer can be divided into two categories: long-term effects and late effects.

Long-term effects of treatment are those that arise during initial treatment and persist after treatment ends. This category includes pain, physical limitations, fatigue, cognitive difficulties, and sexual problems.

Late effects of treatment are usually experienced as new health problems, appearing months to years later. The latter can include lymphedema, hypothyroidism, cardiac or respiratory problems, or secondary malignancies [13]. Despite an outcome of positive prognosis from the treatment of primary cancer these effects often contribute to increased morbidity for cancer survivors.

In this sense, according to the growing number of cancer survivors, the promotion of long-term health needs to be a central goal of survivorship care, ensuring surveillance and preventive interventions necessary to reduce and manage those health risks [12].

Screening for long-term effects can allow for earlier intervention and management of these concerns as well as risk stratification for intervention. Routine follow-up care should include standardized symptom assessments to facilitate earlier intervention in those with persistent difficulties.

Early inclusion of rehabilitation services represents another important component of survivorship care. Rehabilitation may benefit high-risk patients (e.g., frail, elderly, and those undergoing complex surgery), and specialized rehabilitation can help survivors in their physical recovery from primary treatments [14]. Rehabilitation services are especially appropriate for the management of the physical needs of survivors, including pain and symptom control.

The design and implementation of models of care require approaches that are not only disease-focused but take a holistic approach to survivorship care by addressing patients' physical, psychosocial, and spiritual needs.

In this context, cancer survivors need to be educated about expectations after their treatment ends and how they should be monitored for the late effects of cancer

treatment. This must be facilitated by ensuring that their clinicians, including the full spectrum of primary care providers and specialists, as well as allied health professionals, have comprehensive education and training about the long-term and late effects of cancer and its treatment [12].

The same approach has been recommended in the recent update on the ESMO Clinical Practice Guideline on the management of cancer-related fatigue (CRF), released by the European Society for Medical Oncology. The document provides key recommendations on the management of cancer-related fatigue, advising on shared decision-making between patients and health care professionals. The guidelines stress the role of education and counseling as essential for helping cancer patients anticipate and cope with fatigue that may be associated with their disease or related to their cancer treatments [15].

Europe has no formalized indications on how survivorship care should be organized. There are many recommendations and policy efforts, but no generic practical approach has been established yet.

Recently the debate has been focused on the necessity of specialized cancer survivorship clinical structures within or outside the Comprehensive cancer centers (CCCs), to address the need for infrastructures/facilities for long-term follow-up and support of cancer survivors [16].

The challenge is to decide how survivorship care should be organized, whether in specialized survivorship clinics as in the United States, in rehabilitation clinics as in Germany, or according to an entirely different approach [16].

Long-term follow-up is particularly relevant for pediatric and young cancer patients. In the Netherlands, all seven pediatric oncology centers have established a survivorship clinic for survivors of childhood cancer. Care focuses on education, early detection of late effects, and coordination of care for all 5-year survivors of childhood cancer. Risk-based surveillance is based on the Dutch Children's Oncology Group Long-Term Follow-Up Guidelines [17, 18].

In the same context, the PanCareFollowUp is an ongoing EU Founded project aimed at improving the care of young adults who have survived childhood cancer [19].

Large differences persist in health care systems and culture concerning health care between the European countries. However, all European Union citizens should have equal access to optimal survivorship care [20].

Survivorship care needs to be accessible, affordable, and equitable. In this sense further efforts to accelerate the pace at which evidence-based knowledge is translated into improved clinical practice are needed [12].

The Psychological aspects of Survivorship Cancer Care

Cancer and its treatment have a significant impact on the quality of life of patients and their families and carers.

Experiencing cancer has positive effects on a significant portion of individuals, including strengthened relationships, a sense of gratitude or empowerment, and an increased appreciation for life [21]. On the other side, a substantial proportion of

cancer patients and survivors can experience high levels of cancer-related distress and may develop more serious mental health problems such as adjustment disorders, anxiety disorders, and depression [22, 23]. Studies on childhood cancer survivors confirm largely similar findings [24–27].

Distress can result from the fear of recurrence or death, or secondary to physical, social, or practical problems. Indeed, as many as 19% of survivors meet the criteria for post-traumatic stress disorder [21].

The mentioned conditions can negatively impact the well-being and quality of life of cancer survivors and may require specialized psychosocial care. Psychosocial problems also affect the patient's family with a consequent increase in emotional distress among the patient's caregivers.

The impact of psychosocial disorders for patients and families is of paramount importance in oncology since psychiatric morbidity is associated with the reduction of quality of life, impairment in social relationships, longer rehabilitation time, poor adherence to treatment and abnormal illness behavior, and possibly shorter survival [28–30]. Significant levels of burden and emotional distress have been also reported to affect family members and there is evidence that unrecognized and unmet psychosocial needs are an important predictor of psychological morbidity in caregivers in every phase of the illness [28–30].

Patients' and their family supportive care needs must be an important component of quality comprehensive cancer care [31].

Historically, psychosocial support has been neglected in cancer treatment [32, 33]. Access to psychological intervention during survivorship can be difficult, either because of patients' reluctance or because insufficient care is offered [3, 34].

Over the past years, the collaboration between the associations of oncologists, surgeons, radiation oncologists, anesthesiologists, psychiatrists, and other mental health professionals have provided the implementation of guidelines on psychosocial care in cancer in many different countries, included in Europe, the United States, Canada, and Australia [28, 35–37].

According to what is mentioned, recommendations regarding screening, assessment, and intervention to psychiatric and psychosocial disorders are considered mandatory in every cancer center, institute, hospital, including primary care and a key component of the health care system [28].

However, social inequalities still exist, in part because of the lack of resources in several areas of the world as well as the significant economic constraints within the health systems of many countries, including in Europe [3].

The Impacts of Cancer in the Socioeconomic Lives of Cancer Survivors

The fight against cancer can be a broad experience of leaving that goes beyond the cancer diagnosis. One-third of cancer survivors in Europe are of working age and they face several challenges in the social reintegration into society after beating cancer [38]. Deterioration of physical, mental, and social quality of life in

survivorship is strongly connected to precarious situations (e.g., low income, unemployment, and other socially disadvantageous positions) [3, 39].

The main difficulties in the socioeconomic lives of cancer survivors are related to stigma and discrimination, which prevent the effective rehabilitation and social reintegration of former patients. These new challenges have been highlighted during the three consecutive EORTC cancer Survivorship summits in 2014 [40], 2016 [41], and 2018 [42] with the aim to increase awareness of the societal problems. In light of what is mentioned the next section will focus on two main examples of social issues related to life after cancer. The latter concern the return to work and access to loans, mortgages, and life insurances.

Return to Work after Cancer

A total of 2.7 million new cases of cancer (excluding non-melanoma skin cancers) are diagnosed yearly in Europe. More than half of patients experience a cancer diagnosis in working age when career and employment-related issues play an important role in individual and family life [43, 44].

Thanks to the improvements in early diagnostic methods and effective therapeutic strategies, survival rate of cancer patients is growing, reaching 54.2%, 5 years after the diagnosis of a malignant tumor [45]. Of this latter, more than one-third are cancer survivors of the working age [38].

Return to work has a key role in the strategic approach of rehabilitation for cancer survivors, and an increasing number of data is addressing the difficulties of being back to work as a cancer survivor [38, 46].

Several review articles from both the United States and the European Union have summarized return-to-work studies, reporting average return-to-work rates of approximately 64%, with a wide range between 24% and 94% [47–50]). As a result, return to work rates may differ significantly from one country to another and from the employment status either as an employee or as a self-employed [51].

Research shows that the risk of unemployment among cancer survivors is 1.4 times higher than among people who have never been diagnosed with cancer [52]. Overall, studies have indicated a steady increase in return to work with increasing time intervals after a cancer diagnosis [53].

Return to work for a cancer survivor is a major goal, and a very important achievement to succeed in being back to normal life, recovering his/her social role and personal identity with positive effects also on health. Social psychologists have documented how work is important to one self-concept, esteem, and quality of life [54].

However, many cancer survivors face long-term symptoms and impairments after treatment ends. The most frequently reported symptom was a diminished level of energy, described as chronic fatigue or exhaustion, and emotional strain due to the ongoing battle with cancer. This is common across cancer types [55, 56]. The next most reported consequences were other physical, mental, and cognitive health implications [57].

These symptoms and impairments can affect the workability of survivors, making it more difficult to remain in or reenter the job market.

According to the main experiences reported, patients have been fired or forced to quit because of their cancer diagnosis or treatment. Others experienced denied promotion, denied employment as a result of their cancer, and inability to obtain health insurance. In these contexts, on several occasions, the employer lacks empathy and may be resistant to adjust job responsibilities to accommodate the employees needs [57].

Some other former patients noticed issues between coworkers' attitudes toward colleagues as cancer survivors [57].

Differences are reported by some studies, stating that manual work, self-employment, and working in the private sector were factors that negatively affect the return to work of cancer survivors. Studies also revealed that the workload, as assessed by cancer survivors was an important factor that negatively affects their return to work [56].

Some studies also state that being female negatively affected the resumption of work [54]. In addition, having children and/or living with a partner seems to act as protective factors while, being single, widowed, or divorced negatively influenced employment status [54].

Perceived employer accommodation for cancer-related and treatment-related symptoms and side effects, long-term or late effects, and follow-up medical visits has been identified as a strong predictor of return to work [47, 53, 55]. In cancer survivors, a return-to-work meeting with the employer as well as advice from a physician about work, flexible working conditions, counseling, miscellaneous training services, job replacement services, job search assistance, and other relative support were factors significantly associated with a greater likelihood of being employed among cancer survivors in both the United Kingdom and the United States [53, 58]. Studies from European countries, such as Finland, Germany, and the Netherlands, identified younger age, higher levels of education, absence of surgery, fewer physical symptoms, shorter duration of sick leave, male gender, and Caucasian ethnicity as variables that were predictive of or associated with return to work [48, 59, 60].

Against this background, the return to work support should be integrated early into the cancer care pathway, exploring the feasibility of adequate or progressive resumption of work, and raising awareness of employers about working conditions [61–63]. In this respect, keeping in touch with colleagues at work helped cancer survivors to return to work (even partially) quicker. It also allowed a better understanding of colleagues regarding the cancer survivors' limitations and helped cancer survivor limitation and helped them to tailor their work adequately [56, 64].

Supporting cancer survivors in employment-related issues with psychosocial interventions is particularly important, ideally immediately after diagnosis and during treatment [65]. The process should be oriented to a person-centered approach, taking into account determinants, such as diagnosis and prognosis, medical and nonmedical treatments, intra- and interpersonal factors, patient values, aspirations and priorities, the attitude of colleagues, job demands, and so on [3].

Strategies of resumption of work for cancer survivors can be oriented to employees or the work environment and employers. The first approach aims at ensuring the employability of cancer survivors. Work environment-directed interventions aim at adapting workplace environment, equipment, tasks, and working time patterns to the needs of the cancer survivor [3].

Regarding employment and return-to-work issues, there are some good examples of regulations for the protection of cancer survivors and their relatives.

As an example, in 2003 and then in 2007 Italy approved a law stating on the right for cancer patients (working in the private and the public sector) to switch from full-time to part-time positions while under treatment, and to reverse to full-time according to their needs and capability [66, 67]. Within the same legal framework, relatives (caregivers) of cancer patients are given priority over part-time applications as long as there are positions available [68].

The CanCon Guide reported 78 good practice examples of returning to work support policies, systems, programs, and instruments for people diagnosed with cancer. The examples were collected from 13 EU countries, the USA, and Australia. The initiatives showed that return to work is influenced by the institutional context of a country, especially the length of paid sick leave. Besides, the early intervention or paying attention to return to work early in the illness process appeared to be important in every program. Although, the analysis confirms the need for cooperation between different stakeholders, including the cancer survivor and his/her family, the employer, health care professionals, and occupational rehabilitation experts, as an important element for a positive impact on the resumption of the work process.

In this context, another important instrument is the "Rehabilitation and return to work after cancer—instruments and practices" project, commissioned by the European Agency for Safety and Health at Work (EU-OSHA) [55]. The project studied the issues surrounding rehabilitation and return to work after a cancer diagnosis, and the problems encountered by workers affected by cancer and their employers in the EU area. Furthermore, the final report has been published in 2018, including recommendations for instruments, practices, policies, and interventions to successfully support the return to work of workers affected by cancer.

Access to Financial Instruments and the Right to Be Forgotten

Socioeconomic issues experienced by cancer survivors Europe are also related to obstacles to access to financial services, such as mortgages, loans and life, or travel insurance.

Having a history of cancer often represents an obstacle for former patients to access the mentioned instruments. According to the experiences reported by cancer survivors, the main issues noticed rely on the denial directly from the bank, or the need to contract life insurance to ensure the credit [42, 69, 70]. Also in those circumstances, no insurer may agree to provide a contract, other than through charging an additional insurance premium or the warranty exclusion provision.

Bankers and insurers have difficulties assessing the risks associated with such a complex disease and its risk of relapse. As the progress of cancer treatments is rapidly improving the prognosis of many patients, up-to-date information is still often lacking, and risk assessments are made on outdated data or models.

The inadequacy of specific criteria uniformly applied by private actors contributes to generating a fragmented assessment practice, mainly self-regulated by the same companies, with a lack of transparency and monitoring control.

The exclusion of cancer survivors to contract life insurance and the other financial instruments, make property ownership difficult or even impossible in some countries. This situation can induce a double penalty feeling for cancer survivors, hindering many of them from coming back to a normal life. Beyond successful treatment, social and professional reintegration is important to restore a sense of normalcy after surviving cancer, which is key to a patient's remission.

In this regard, further studies and investigation should be performed to investigate the impact of those denials as indirect issues connected to the financial stress faced by cancer survivors and their families [71].

To face this issue, in the last years, France, Belgium, Luxembourg and the Netherlands adopted legislative initiatives recognizing a Right to be forgotten for cancer survivors. The latter have in common the principle to ensure access to financial instruments for cancer survivors once they achieve complete remission.

The provisions state that in the context of the mentioned financial instruments, the period beyond which no medical information relating to the previous cancerous disease can be collected or taken into consideration by insurance organisms may not exceed ten years after the end of treatment. The laws also include a list of exceptions for cancers with an excellent prognosis having shorter delays to recognise the Right to be forgotten. Besides France, Luxembourg and the Netherlands introduced a reduced delay for cancers diagnosed before the age of eighteen (in Luxembourg) or twenty-one years old (in France and the Netherlands) benefit of the Right to be forgotten five years after the end of the active treatment, with the condition of no relapse all along the same period.

Recently, the Portuguese Parliament voted on a draft proposal that could lead to implementing the Right to be forgotten in Portugal by summer 2022.

Concerns about the socioeconomic issues experienced by survivors of cancer across Europe have been raised also at the EU level. In this regard, an important step forward was the inclusion of the Right to Be Forgotten as a priority to tackle in Europe's Beating Cancer Plan, presented by the EU Commission in February 2021 [72, 73]. Lately, the Interim Report of the Mission Board for Cancer included the Right to be forgotten among the recommendations to the EU Member States to counteract discrimination and to ensure equality [72, 73].

Against this background, a pan-European solution based on the implementation of the Right to be forgotten is the best approach to tackle the issue. The EU Action would provide a common regulatory framework among the Member States to avoid discrimination and ensuring equality among EU citizens who experienced cancer.

Conclusion

In the aim to highlight the need to prioritize cancer survivorship issues in the European area, the contribution examined some key aspects related to the challenges of life after cancer. Describing data, research, and the main policies ongoing, the analysis provided an overview of the complexity of a health care strategy, with a multidisciplinary approach and patient-centered orientation.

Facing the increasing number of cancer survivors, improvements in cancer care are needed to ensure the highest standard of quality of life, promoting equality, social inclusion, and the dignity of cancer patients and cancer survivors.

As part of the rehabilitation approach, the societal issues (such as access to work, education, insurance, loan, mortgage, and financial toxicity) faced by long-term cancer survivors should be evaluated and prioritized in the survivorship research agenda.

Besides, early implementation and good communication between all relevant stakeholders are essential for effective rehabilitation interventions, and cancer survivors' care programs.

Another important aspect concerns the need to increase the collection of data and further research, to assess the effective status of cancer survivors in Europe and share good practices between the EU Member States.

Against this background, the Interim Report of the Mission Board for Cancer confirmed the necessity to develop an EU-wide research program and policy support to improve the quality of life of cancer patients and survivors, family members and carers, through cross-sector interventions, including regulatory and social measures. Moreover, the initiative stressed the need for a common EU project to collect and share data for cancer research [72, 73].

Recently, the European Academy of Cancer Sciences (EACS) and several European organizations provided a list of recommendations for the implementation of a mission-oriented approach to cancer in Horizon Europe. The document included the necessity to improve survivorship research as a key element to develop effective survivorship care models [16].

Among these initiatives, it is important to mention the release of the European Code of Cancer Practice [74]. The document is a citizen and patient-centered manifesto of the core requirements for good clinical cancer practice, to improve outcomes for all of Europe's cancer patients. The Code focuses on informing and assisting cancer patients at all stages of their cancer journey. The quality of life, together with cancer survivorship and rehabilitation are among the 10 key overarching rights that patients should expect from their health system. The initiative has its origins in the European Cancer Patient Bill of Rights, and it represents an example of a bottom-up policymaking measure, empowering cancer survivors and improving cancer health care and rehabilitation for their better quality of life.

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4 Follow-Up and Long-Term Follow-Up of Cancer Patients: Who is in Charge, why, when, and how…: Introduction: The Evolution from "Surveillance" to "Survivorship Care"

Stefan Rauh

Cancer patients are not only steadily rising in number across Europe, but they also have a much higher probability to live longer. This is particularly true for childhood cancers, which can be cured in 75–95% of cases [1]. Since the beginning of this century, adult cancer patients have been shown to expect at least a 60% 5-year survival, while 30–40% survive 20 years or more [2]. The decline in mortality and rise in long-term survival are continuing. 2020 has seen a significant decline in cancer mortality in the United States, mainly due to a sharp decrease in lung cancer mortality [3]. These advances are due to early detection, more efficient treatment strategies both in active treatment and in supportive care [4]. Surveillance for cancer recurrence and secondary malignancies also has the aim to prolong survival and cure through rapid reintervention. The underlying evidence remains however scattered and overall low [5]. Still, these endpoints remain paramount in patients' and physicians' beliefs of the importance of early follow-up and surveillance [6].

As more and more patients better survive their cancers, late treatment effects become of greater concern. Secondary leukemia may arise between 5 and 10 years after certain chemotherapies, while solid malignancies may start occurring 10 years after the initial radiotherapy. Cardiotoxicity after anthracyclines or irradiation also occurs late [7–10]. Oncologic surgery may induce lymphedema, neuropathy, or organ dysfunction (e.g., incontinence, erectile dysfunction) at distance from the intervention [11, 12].

The recognition of both treatment sequelae and secondary malignancies has led to the concept of "Long-Term Follow-Up" (LTFU) of cancer patients. LTFU should

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assess the patient's general health condition, timely screening for late effects and secondary malignancies, and provide adequate treatment for these whenever possible [13]. LTFU was originally developed and proposed in childhood cancers, who face a higher rate of morbidities, secondary cancer, more rapid aging, and a lower life expectancy as adults, even when cured [14–16]. These patients were and still are mostly followed-up in highly specialized cancer treatment centers for years—and often even after becoming adults, questioning a reasonable timing and degree of transition to regular medical care and surveillance by a primary care physician. In Europe, there is an estimate of 300000–500000 childhood and young adult survivors [17].

Today, more adult cancers are cured or face chronic cancer conditions with significantly prolonged life expectancies. In the United States, an estimate of 15, five million cancer survivors have been estimated for 2016, and more than 26 million are expected in 2040 [18]. Thus, the concept of LTFU has also increasingly applied to this much larger population.

General post-treatment follow-up (FU) or *surveillance* was traditionally mainly focused on the early detection of recurrence and early treatment sequelae with an estimated interval of 5 years after active treatment. This was performed by a specialist, often an oncologist (medical, radiation, or surgical). Research in survivorship is replacing habits with evidence. The therapeutic landscape of cancer treatments evolves rapidly. Thus, surveillance has undergone continuous changes, but still remains often difficult to define in its benefits according to proven endpoints [5].

Side effects arising during treatment may remain chronic conditions with variable extension and resolution in time ("long-term side effects"). They may also arise with variable latency after the end of treatment ("late effects"). Genotype, age, comorbidities, treatment combinations and sequences, and other factors may lead to individually different presentation, amplitude, and timing of these effects [19]. As a consequence, there is no clear transition from the follow-up to long-term follow-up, neither a clear distinction in tasks.

Ever after the seminal report of the Institute of Medicine in 2006 and the emergence of a holistic approach towards the Cancer survivor, the range of items included in FU/LTFU has largely risen [20] with the addition of preventive measures concerning a healthy lifestyle, as well as psychosocial and community aspects (including professional reintegration, etc.) [21–23].

The terms of follow-up and long-term follow-up may be used synonymously with survivorship care in many publications—whenever they do not allude to selected endpoints compatible with the more traditional surveillance.

Here are some definitions for FU LTFU and survivorship care:

Definition of Follow-Up
"Monitoring a person's health over time after treatment. This includes keeping track of the health of people who participate in a clinical study or clinical trial for a period of time, both during the study and after the study ends." [24].

Definition of Surveillance
"In medicine, closely watching a patient's condition but not treating it unless there are changes in test results. Surveillance is also used to find early signs that a disease has come back. It may also be used for a person who has an increased risk of a disease, such as cancer. During surveillance, certain exams and tests are done on a regular schedule. In public health, surveillance may also refer to the ongoing collection of information about a disease, such as cancer, in a certain group of people. The information collected may include where the disease occurs in a population and whether it affects people of a certain gender, age, or ethnic group." [24].

Definition of Long-Term Follow-Up
"Long-term follow-up for children's cancer survivors typically begins when patients are in remission and fully recovered from the immediate effects of treatment. Often, this is about 2 years after completion of treatment. In long-term follow-up, the goal is to help former patients stay as healthy as possible and to do well in school and eventually at work. It is important for all survivors to continue to have regular medical care for life. This is often called survivorship care" [25].

LTFU in a research context: "Long-term follow-up begins when the protocol treatment is discontinued, treatment toxicities have resolved, and the response to therapy has been determined. The purpose of long-term follow-up is to assure continued medical surveillance and allow meaningful end-results reporting. Study endpoints are dependent on having meaningful data on items such as recurrence, disease status, survival, long-term adverse events or new malignancies." [26].

Definition of survivorship *care*: "Prevention of new and recurrent cancers and other late effects, surveillance for cancer spread, recurrence, or subsequent cancers, assessment of late psychosocial, physical, and immunologic effects, intervention for consequences of cancer and treatment (e.g., medical problems, symptoms, psychologic distress, financial, and social concerns), coordination of care between primary care providers and specialists to ensure that all of the survivor's health needs are met, planning for ongoing survivorship care" [27].

In common communication between different caregivers and patients, "follow-up" remains a commonly used term with more or less clearly defined content, probably according to the caregiver's own judgment and willingness to encompass and the follow-up framework.

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5 Models of Long-Term Follow-up for Cancer Patients: From Children to Adults, from Simple to Multi-Modal

Claire Berger and Charlotte Demoor-Goldschmidt

Regular care through the early detection of possible sequelae, therapeutic education, and management of psychological difficulties could have a positive impact on the quality of life and long-term health of former patients cured of cancer. However, not all patients benefit from it and, when considering CCS, up to two-thirds do not return for long-term follow-up (LTFU) consultations when offered [1–3]. There is an added problem in CCS follow-up which occurs when the patient has to transfer from pediatric to adult health services, which means a change in the specialists treating them.

In developed countries, the rate of survival after childhood cancers has reached up to 80%, compared to 87% following cancers in adolescence and young adulthood. However, the late-onset effects of their early cancers and associated treatments concern adult survivors [4]. It is currently estimated that one young adult (between the ages of 20 and 39 years) in 530 has had cancer during childhood [5]. In all the population, a combination of increased cancer incidence and improved cancer treatments has led to a growing population of people living with, and beyond, cancer. However, the downside of this is that therapies are sometimes very aggressive in terms of complications. Cancer survivors are at high risk of early mortality, chronic morbidity, and secondary cancers, when compared to the general population. Adults cured of pediatric cancer, identified in the international literature as "childhood cancer survivors" (CCS), are at higher risk because of a higher

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sensitivity to treatments and a longer life expectancy [6, 7]. Nevertheless, adult cancer survivors also have to face complications and sometimes these complications can occur later in life [8, 9].

If, at first glance, we focus on the physical dimension, it is because the potential somatic sequelae of cancer and its treatments are frequent, extremely varied in type and intensity, likely to affect all organs, more particularly the cardiovascular, endocrine, renal, musculoskeletal, cutaneous, and neurocognitive spheres. Despite undeniable progress, cancer remains very worrying, being cured of cancer remains a source of morbidity and mortality [10, 11]. Concerning CCS, an original article in the New England Journal of Medicine published in 2006 is still a reference. It analyses, with an average hindsight of 17.5 years, more than 10,000 former patients cured of pediatric cancer, compared to their healthy siblings. More than 60% of these patients had at least one chronic complication and in 27.5% of cases it was a severe, life-threatening, or fatal complication (so-called grade 3 and 4 sequelae) [12]. For the moment, the state of health of adults cured of childhood or adolescent cancer does not improve with time. In fact, the prevalence of physical complications continues to increase throughout the lifetime of individuals, without reaching a plateau [13]. In other words, the increasing distance from oncologic treatment does not reduce the risk but amplifies it, which justifies life-long follow-up of this "at risk" population. Similarly, the significantly increased risk of a second primary cancer must also be taken into consideration, since it is estimated to affect 36% of cancer survivors [14–16], justifying prevention and screening measures specially adapted to this population.

This increased survival rate has led to a greater importance of potential long-term sequelae, and to the interest and importance of survivorship. In 2020, 327 articles were found in the Pubmed database with "cancer" and "survivorship" in the title, versus approximatively 108–136 between 2015 and 2018, under 100 in the years before, with less than 60 up to 2010 and less than 10 before 2006.

Even if all the complications of cancer and its treatment cannot be prevented, many of these can be early diagnosed and can be effectively treated in the same way as certain classic complications. Such conditions include breast cancer complicating mediastinal radiotherapy during childhood [17] or young adulthood [18, 19]; anthracycline heart disease [20]; and osteoporosis or early menopause induced by chemotherapy and/or hormone therapy, frequently used for breast or prostate cancer, or during corticosteroid therapy [21–24]. Early counseling and early screening can improve morbidity and mortality. With this aim in mind, several scientific societies developed recommendations for childhood cancer survivors and an effort is made to harmonize them.

Psychological or psychosocial complications are less known, and less understood. After childhood cancer, real post-traumatic stress states were found long after the end of the illness [25, 26]. These data were confirmed by other teams [27, 28]. The social, educational, sexual, and fertility dimensions were also explored in relation to the quality of life [29–31]. These sequelae are also found among adult cancer survivors, but their characteristics are often different as cancer may have been diagnosed and treated when the patient already has a job and a family [32–35]. Fatigue

is another frequent and insiduous complication as it is not palpable but it significantly decreases the quality of life [36–40].

Regular care through the early detection of possible sequelae, therapeutic education, and management of psychological difficulties could have a positive impact on the quality of life and long-term health of former patients cured of cancer. However, not all patients benefit from it and, when considering CCS, up to two-thirds do not return for long-term follow-up (LTFU) consultations when offered [1–3]. There is an added problem in CCS follow-up which occurs when the patient has to transfer from pediatric to adult health services, which means a change in the specialists treating them.

To date, cancer survivorship is not organized in all countries, and particularly not for adult cancer survivors. Some specific programs do exist for certain conditions, for example, after Hodgkin disease, breast cancer [32], head and neck cancer [41], and pelvic cancer [42–44], mainly under the form of a trial. This sort of organization is able to provide support to patients after specific cancers and is easier to organize as the difference between each patient is limited and the follow-up plan care is harmonized. Some clinics have developed LTFU for adult cancer survivors, but this is still quite rare [45].

The first models of LTFU care have been developed for childhood cancer survivors and they are actually well developed in several countries [46]. To date, most LTFU of CCS has been done by pediatric oncologists [47, 48]. For many people, and also for patients, the clinician responsible for their initial treatment continues to see them, but at a decreasing frequency. As the risk of disease recurrence falls, more emphasis is placed on LTFU.

For all these cancer survivors, the place of the general practitioner has been raised [2, 49, 50], more and less with a nurse with a central role in therapeutic education, coordination [51–53]. The place of dedicated LTFU clinics, in terms of interest and costs, is also frequently questioned.

Models of LTFU care for CCS have been driven by the patient, general practitioner (GP), nurse, or medical specialist and conducted either in a LTFU clinic or in physician offices [48, 52, 54–62]. LTFU in specialized late-effect clinics offers optimal and standardized care for CCS, based on current guidelines, recommendations, and research trials [63–71].

Two general models have involved either the GP conducting follow-up without sustained contact with a primary cancer treatment center or late-effect clinic (GP only), or the GP working in close collaboration with practitioners in such facilities (shared care) [56]. Some authors have proposed that the primary care physician should take over follow-up care once the risk of intermediate-term late effects and cancer recurrence are low. In the shared care model, the GP cares for the individual, but the oncologist or LTFU center remains available for consultation [72]. Very close collaboration is essential for survivors with a high risk of developing late effects and who might need to visit the cancer center regularly. The role of the GP increases as oncologists always have new patients actively suffering from cancer and because the number of survivors is still increasing. In several places, there are no LTFU consultations and the GP alone is required to organize the follow-up.

Every cancer survivor and their primary care provider should receive a summary of the disease and treatments received, as well as an individualized survivorship care plan, following the curative treatment. Even with these documents, studies show that it is not enough to be sure that personalized screening and follow-up are done. Some of the barriers are as follows: not enough time; patients do not regularly visit their GP and when they have a consultation, it is when they have a problem (this is mainly reported in young adults); GPs and patients do not remember the survivorship care plan; and there may be difficulties in organizing the different follow-up exams [73]. Advanced practice nurse and telephone counseling can increase adherence, with little or no cost per additional survivor [74].

As a typical example, we present the results of a French study which evaluated the level of satisfaction of CCS and their GPs, with a LTFU consultation process that involved joint consultations between survivor, pediatric oncologist and adult internal medicine specialist. The aim of this joint consultation was to organize transition between child and adult health services and to establish the passport for LTFU. Of the 150 survivor participants in the LTFU, 120 (80%) completed the satisfaction form, with 107 (89%) reporting satisfaction. As a consequence of the consultation, 48 participants (32%) expressed a strengthening in their follow-up. Of the 79 survivors who sent recommendations, 76 (96%) reported reading them, most ($n = 68$, 86%) found them useful, and 56 (71%) followed the recommendations. Of the 107 GPs of the survivors, 82 (77%) reported that they had been poorly informed about the long-term complications for their patients after chemotherapy, and 93 (88%) appreciated having a hospital contact available for these patients [2].

Several studies have suggested scores to screen patients with specific needs (based on specific treatments, such as radiation therapy, anthracycline, bone marrow graft, or specific diseases, such as cerebral tumors) [45, 65, 75]. Several guidelines recommend risk-stratified LTFU for CCS survivors [53], but none of them are able to include the risk of psychological distress.

New models are developed using the informatics like a web-based intervention for pediatric brain tumors targeting psychosocial functioning and late effects [76], educational personalized and online course linked with data recorded in the childhood cancer register (submitted article) [Berger C, Casagranda L, Sudour-Bonnange H, Massoubre C, Dalle JH, Teinturier C, Martin-Beuzart S, Guillot P, Lanlo V, Schneider M, Dal Molin B, Dal Molin M, Mounier O, Garcin A, Fresneau B, Clavel J, Demoor-Goldschmidt C. Personalized Massive Open Online Course for Childhood Cancer Survivors: Behind the Scenes. Appl Clin Inform. 2021 Mar;12(2):237–244. doi: https://doi.org/10.1055/s-0041-1,725,185. Epub 2021 Mar 24. PMID: 33763845; PMCID: PMC7990573]. Other groups propose a shared post-cancer medical record with interface for the patient and her/his different doctors [77, 78] with more and less a reminder function of the tests to be performed addressed to the patient and her/his registered doctor (software which is actually tested in Western France) or dedicated applications and web informations [77, 79, 80]. These are useful tools, but they do not remove all the barriers [81]. The use of teleconsultations has also received a positive response in some survivors who were not able to attend LTFU consultations [82].

There is a lack of evidence for the best way to organize LTFU care. The different traditional approaches found in the literature are as follows:

- Care delivered at the initial cancer center.
- LTFU clinic care. This may be for all survivors or for survivors of specific cancers as part of dedicated programs.
- Shared care between the initial cancer center or LTFU clinic and local hospital or primary care physician.
- Care from a specialist nurse.
- Self-management with professional shared care.

Survivors are all different and face LTFU differently. Several models were proposed to organize LTFU based on the risk of developing severe or multiple sequelae, but these are not able to predict some complications, such as fatigue, psychological distress, and social and intimacy difficulties. A common point that emerges from all these studies is the need for a personalized follow-up that depends on the sequelae already present and the risk of subsequent complications. This requires many health professionals. On a purely medical level, the professionals most in demand are cardiologists, endocrinologists, and fertility doctors, followed by orthopedic specialists, gynecologists, dermatologists, ear, nose, and throat specialists, nephrologists, respiratory specialists, neurologists, dentists and stomatologists, and rheumatologists. From this non-exhaustive list, it can be seen that almost all specialists can be involved. However, this may not be sufficient to meet the needs of patients who, depending on their time of life, may also need the support of a psychologist, a social worker, a physiotherapist or an accompaniment for an adapted sports activity, a dietician, an occupational therapist, a neuropsychologist, a speech therapist, or a sexologist [83–85].

From all the different experiences with different survivors (different ages, from child to adult, different cancers, and different organizations), no evidence-based guidelines exist on how to organize LTFU care [53]. However, the same conclusion is reached: the critical need for a multidisciplinary approach for cancer survivors, and the need for an aware professional who is (1) knowledgeable about the late-onset effects of cancer treatment and (2) able to deliver a global analysis, who can be, for example, an oncologist, a general practitioner, an internist or any physician who is interested [2, 45]. No single organization has shown its superiority over another, even if some studies suggest that CCS knowledge is better in LTFU clinics [86, 87]. It seems evident that for some patients, because of the severity of sequelae or the number of complications, that a specialized and dedicated LTFU consultation is necessary and many countries have already adopted this model, particularly for CCS survivors [53]. However, distance to the clinic for survivors has often been raised as a problem with this approach [88]. Here, for some patients, teleconsultation may be useful to deliver specialized recommendations which can then be followed by the patient, with the help of their GP. The literature indicates that follow-up based only on GP support is not feasible for all survivors. There is a need for a place where they can get specialized advice or assistance, and where they can be referred

to benefit from the expertise. Moreover, knowledge is not static and further studies are necessary, whether on the means of follow-up (such as screening method and frequency) or on treatments used in the case of discovery of complications, or as preventive measures. These studies can only be carried out under the impetus of a dedicated team. While dedicated LTFU may not be indicated for all the survivors and might be too expensive, its presence is necessary for at least some specific survivors therefore research should continue on this theme.

To date, in many countries, LTFU care is organized by individual centers, rather than via a national, cooperative effort. This leads to geographical disparity in care. Improved solutions are needed, with an emphasis on transitioning survivors to appropriate care beyond the pediatric age. Nevertheless, patient needs are different, even after the same disease. The nonmedical determining factors found are patient age, socio-professional integration, and place of residence [82]. Due to the diverse needs of cancer survivors, decision-makers must consider this when considering a homogenization of practices, and they should allow a certain flexibility in LTFU organization throughout the lifespan of the patient.

In conclusion, and in line with the recent review of the literature from a panel of engaged international professionals in LTFU care for CCS [53], a successful model of LTFU for CCS and adult cancer survivors must fit certain criteria. It must be multidisciplinary to cater to the different needs of survivors (medical and paramedical professionals) and have the flexibility to adapt to the different survivors and coordination of care. For good adherence over time, the roles of the different professionals need to be well-defined. The value in the addition of a key worker or online tools requires further study, particularly into the financial costs of this global LTFU care. The last key component is the education of survivors and professionals, to increase their knowledge about the risks of late-onset cancer and treatment-related effects. Lack of it is often found as a barrier to LTFU care and screening. Patient empowerment and awareness are important factors on which we can act, to allow survivors to take over responsibility for their health.

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Who Should Be in Charge of Survivorship Care?

6

Stefan Rauh

What Does Survivorship Care Mean?

Traditionally, medical, but also radiation and surgical oncologists were (and often still are) in charge not only for the active treatment but also for follow-up care of their cancer patients. Often depending on the oncologist's motivations, willingness, and capacities at the end of active treatment or a more or less short phase of surveillance, patients returned to their primary care physicians, often without the necessary guidance and coordination of follow-up [1]. This harmful gap in the continuity of care was well described in the seminal report: "Lost in Transition" which was published by the US Institute of Medicine in 2006 [2]. The report has also defined the multimodality of survivorship care and initiated a search for sustainable and holistic survivor care models.

Change in the general policies towards transition and share of responsibility in cancer survivor care is however imperative due to limited specialist resources facing a growing number of cancer survivors. Scarcity of human resources is a motor in the share of survivorship care among different disciplines and modalities [3–5]. Research in the field of survivorship care has also tried to determine whether one model of care was superior over the other—or whether models were comparable in outcomes while more convenient or less expensive on the other hand.

Cancer follow-up refers to the process of care delivered after the completion of primary cancer treatment, with the main objective being surveillance and prompt detection of recurrence or new cancers, in order to optimize further treatment outcomes [6]. As explained in the introduction, the definition of follow-up care (survivor care) should include more dimensions:

Secondary objectives of follow-up programs include identifying and managing side and late side effects of cancer and its treatment, providing informational and

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psychological support, and relevant referrals to rehabilitation and other healthcare services [7].

From the patient's perspective, follow-up is also meant to give reassurance, help with coping and enable involvement in survivorship care [8].

I will use the terms of long-term follow-up (LTFU)/follow-up (FU) and survivor care (SC) synonymously in this chapter, mostly using the term FU as it is the term used in most publications.

As explained in the previous chapter, there are a variety of FU models (oncologist-based, primary care provider (PCP)-based, specialized nurse-based, survivorship clinic-based, patient self-managed, or a combination of several, which share certain features and have possible advantages and disadvantages.

In current practice, it will mostly be an oncologist (medical, radio, or surgical oncologist) who will initiate the follow-up. Traditionally, he will also pursue FU care. Less often a general surgeon, organ specialist (gynecologist, gastroenterologist, etc.) will carry out follow-up care. This includes consultation of the patient with a physical exam, prescription of diagnostics, referral to (other) specialists, and as well as—when detected—treatments in case of long-term or late effects. Sometimes, the oncologist will also manage non-oncological comorbidities "along the line" as they remain the caretaker scheduling their patients for visits in regular intervals [8–11].

A Surveillance, Epidemiology, and End-Results (SEER) analysis of follow-up of breast cancer patients covered by Medicare in the United States revealed that follow-up was managed in 80% of the time by medical oncologists, 46% of the time by a surgeon and 39% of the time by radiation oncologists. Whereas medical oncologists were predominant as follow-up providers in patients with locally advanced disease and a history of chemotherapy, frail and older patients had a higher probability of non-specialist follow-up care [11]. This might reflect a reasonable pattern to individualize follow-up according to the probability of recurrence and need of systemic treatment on the one hand, and the patient's improbability to benefit from further treatment on the other. This study did however not detect a systematic pattern of combined or single specialist follow-up. There was also no homogeneity concerning the frequency of scheduled follow-up visits [11]. An update 4 years later did not detect any difference to these results [12].

Who Fares Better?—Perceptions of Oncologists, Primary Care Physicians, and Patients

Most studies confronting perceptions have compared oncologist/specialist with primary care physician FU.

Medical Oncologists' Perception of FU

Oncologists in specialized treatment centers have traditionally provided FU care [13]. In several surveys, oncologists consider they should be in charge of the follow-up of their cancer patients. During active treatment, oncologists often have

developed a close relationship with their patients. Based on their knowledge in internal medicine, they also will have often initiated treatments for non-oncologic disorders, as they arise along with antineoplastic therapy. In certain cases, they will already continue to provide treatment beyond the "active" treatment phase (i.e., endocrine treatment in breast cancer). They believe patients to prefer follow-up to be provided by them as specialists rather than general practitioners, whom they do not consider knowledgeable enough to take over [14–18]. They also consider themselves to offer specific skills for follow-up [12]. Thus, they are often reluctant to delegate patients to PCPs or others for FU [19]. This is particularly true for the first 5 years of follow-up [20]. Oncologists acknowledge a role for general practitioners, particularly in psychosocial domains. Interestingly, handling diabetes, hypertension, or other aspects of internal medicine are considered within the oncologists' management skills and provided so as to avoid unnecessary traffic for the patient between different physicians, as they are seen by the specialist in regular tight intervals, anyway [1]. Medical specialists consider PCP important in sharing the management of psychosocial concerns [19, 21–24]. There is no clear pattern of over- and under-prescription in both specialists and PCPs when compared to guideline-oriented FU. Different studies come to different conclusions. Prescription behavior seems rather based on individual caregivers than on specialty [11, 25–27].

Primary Care Providers'(PCPs') Perception of FU

As the number of cancer patients and cancer survivors continue to rise, a continued follow-up by an ever more limited oncology workforce is increasingly unfeasible [28, 29]. Some FU need specialist care (e.g., cystoscopies for bladder cancer), many may however safely be performed by other caregivers [1].

This has led to a shift in follow-up towards primary care physicians at the end of active treatment, which has in some European countries become systematic. In the United Kingdom and the Netherlands, the PCP is the main health provider for secondary care [30]. In a French study on Hodgkin's disease survivors, PCPs were significantly more solicited during the first 4 years of follow-up, even outside of the context of systematic follow-up care [31]. In a Dutch trial, cancer survivors also significantly had more primary care contacts within the first 5 years of follow-up. Interestingly, this was especially the case in younger patients without chronic diseases [30]. In current guidelines, regular assessment of cancer patients is proposed by either an oncologist, a PCP, or both [32–34].

The shift towards PCPs is not just a logical evolution of the oncologist's workload with increasing cancer patients and their rising life expectancy. As oncologists mainly follow-up for recurrence and treatment sequelae [35], many specific needs such as cardiovascular or diabetic conditions (cancer treatment-related or not) or lifestyle issues are better recognized and more often handled by primary care physicians [36].

Some studies have examined whether standards of follow-up care have been respected, according to underlying national guidelines. In a Canadian cross-sectional survey, 21 "need-to-know" breast cancer guidelines were rated by 82

PCPs and nurse practitioners as implemented, aware of but not regularly implemented or unaware of. Only less than half of the guideline recommendations (46.4%) were regularly implemented. Screening for prevention and recurrence had better scores, whereas knowledge and practice gaps were highest concerning recommendations on screening and management of late-term effects [37].

Primary care physicians do not necessarily feel comfortable with the role as main follow-up provider, with no formal education concerning follow-up care provided in current curriculums. In a survey among PCP, 82% believed that primary care guidelines for adult cancer survivors were not well-defined, and 47% complained of inadequate preparation and lack of formal training in cancer survivorship [38, 39]. Some studies found little more than half of the participating PCPs felt comfortable participating in FU, while a same percentage did not wish to manage FU entirely [24, 40–42].

Lacks of time, compensation (including reimbursement issues and patient trust) are other barriers to shift FU to the hands of PCPs [41, 43, 44]. Delays in re-referrals to specialists and rapid access to diagnostic procedures in case of need of exams are a major concern for patients if FU is managed by PCPs [45]. General practitioners reported to have largely relied on "learning by doing" and "hit and miss," with highly variable individual knowledge gaps [44]. In a Canadian survey, PCPs declared being overwhelmed trying to keep up to date through the mass of data and guidelines among all the other primary care topics. They expressed anxiety over dealing with cancer survivors instead of experts. Time constraints and additional workload due to the shift of responsibility were of concern. PCPs felt being taken "out of the loop" while their patients were treated in cancer units and expressed the desire for posttreatment protocols. Providers were interested in empowering survivors to share responsibility or to coordinate their own care, and suggested that guidelines or care plans be provided to patients and providers alike [46]. This survey however did not compare outcomes with a comparable group of specialists. Among 227 general office or clinic-based general internists implicated in follow-up care, four areas of survivorship care were asked (monitoring for cancer recurrence, managing late side effects, sexual function, and mental health). Multidimensional follow-up was only provided by 24% of the participants [38]. Another survey in 298 breast cancer patients from Colorado and Arizona did not find a significant difference in the implementation of the ASCO (American Society of Medical Oncology) guidelines (with items checked however largely limited on recurrence screening [47]. In a large US-based survey, a significant number of PCPs lacked awareness concerning late side effects such as late cardiac toxicity, fertility, neuropathy, or secondary malignancies after exposure of frequently used cytotoxics in contrast to oncologists. Clear guidance from the oncologist to the PCP was considered essential in case of transition of FU [48]. Professional training programs and the development of "Onco-Generalists" have also been proposed [49]. Today, a range of educational tools for PCPs willing to specialize in follow-up care exist, mainly in the Anglo-Saxon language [50–52].

Patients' Perception of FU

Patients' definition of survivorship care varies strongly, as do expectations on the contents and value of follow-up visits.

At least during the first years of FU, patients' major concerns and anxiety stem from the fear of recurrence. FU visits are seen to reassure, provide confirmation of remission or early detection of recurrence (in the perspective of improving survival) [53–57]. The role of intervals between FU visits varies as some patients find longer intervals reassuring while others do not seem to see an influence on their level of anxiety while yet others see their anxiousness increased [53–55]. Clinical tests provide temporary reassurance, with a rebound in anxiety after a certain time or before the next FU date [53–55, 58–60].

Patients tend to attribute the capacity to provide surveillance with qualified information on prognosis rather to oncologists then to general practitioners [61, 62]. Professional interpretation of test results and information on prognosis of their neoplastic condition are valued in specialists and hospital-based follow-up [58, 59, 61]. Patients express their need for rapid access to exams and expertise when needed and their interpretation by professionals [55, 58–60]. Surprisingly, in some studies concerning FU, patients declared no increase of anxiety due to regular consultations, and a low level of anxiousness in case of frequent exams. Stress and anxiety were reported to be minimal when compared to the follow-up benefits received by routine surveillance visits. Patients declared deep satisfaction to hear confirmation of their ongoing remission. They also expressed however their wish to be informed of negative test results or recurrence, and incurable disease [61, 62].

In a lower number of studies, patients declared dissatisfaction with unmet expectations in the exchange of information concerning prognosis, or treatment sequelae, including a lack of being asked relevant questions or receiving satisfactory answers concerning their quality of life [61, 63]. Patients noted the absence of emotional support. Anxiety over tests and consultation was highest early in FU, in younger patients and particularly in patients with young children [61, 64].

In a large survey among early breast cancer survivors from a SEER database, a majority of patients expressed a preference for PCP concerning the handling of comorbidities and general preventive care, whereas they attributed the task of cancer follow-up and screening for recurrence and other cancers to their oncologist. However, a large proportion of women with higher education preferred that oncologists be in charge of all services [36]. The authors concluded that patient education about different competencies of PCP and oncologist was needed. In a Dutch study, patients expressed high satisfaction with specialist (surgeon) led follow-up and expressed higher willingness for a transition to PCP-led follow-up only in the case of low risk of cancer recurrence [65].

In several studies, FU by specialized nurses has been compared with physicians. Results showed no significant differences in endpoints, but a trend towards higher patient satisfaction concerning psychosocial support, support in coping with the

disease, improved access to care, continuity and time as compared with physicians (mainly PCPs) [66–71]. In a randomized study in colorectal cancer survivors, survivors in the experimental group receiving nurse-led survivorship care were more satisfied with care and empathy. Psychosocial issues were rather discussed with a clinic-based specialized nurse than a PCP [66, 72].

Some patient perceptions were independent of the caregiver:

Psychosocial support is seen as important, even though patients acknowledge that providing comprehensive integration into routine FU is difficult in the context of time constraints [55, 73].

No matter who the responsible caregiver is, a long-term relationship with one correspondent as caregiver correlates with higher confidence and satisfaction of FU consultations. This also includes a good relationship and continuity in FU care [58, 63, 74, 75].

Patients with regular follow-up expressed higher satisfaction as compared to patients with infrequent consultations. Patients wish emotional reassurance from follow-up visits. "Confidence" and "trust" in their caregiver are often expressed values motivating the desire for follow-up care [61, 62].

Some patients mentioned parking facilities, distance from home, or less expensive visits as reasons for their preference, others the length of consultation [76, 77].

In summary, patients expected expert follow-up related to the reassurance of persisting remission, early recurrence, and professional information on prognosis, while expressing need for holistic management of their health issues with psychosocial support from a caregiver with close relationship—also providing sufficient time during consultation. Rapid access to consultations and exams without unnecessary delays are a concern when shifting FU from oncologists/specialists to other caregivers.

Who Fares Better? Evidence

Survival Benefit According to the Chosen FU Model

There are few studies providing data on overall survival (OS) differences in specialist-led versus PCP- or nurse-led follow-up. One large study on breast cancer patients [78] and colon cancer patients [79] showed in a pooled Cochrane meta-analysis no significant difference in OS, still favoring specialist-led follow-up [80]. Importantly, in both studies PCPs (as well as specialists) were provided guidance through a follow-up protocol. (the use of the follow-up protocol for colon cancer patients was not compulsory).

Overall survival (OS) is an ambitious study endpoint: due to the higher cure rates and longer follow-up duration, a need for high patient numbers and strong homogeneity of the comparative groups, the endpoint may be difficult to reach. Overall evidence was considered of low certainty in a Cochrane review [80]. Outcomes may be difficult to compare as follow-up varies according to the type of cancer and the detailed circumstances of follow-up provided.

Progression Free Survival and Early Detection of Recurrence

Progression-free survival and early detection of recurrence have been compared in various studies between models of FU.

Recurrence was compared in a Swedish randomized study in 264 early breast cancer patients (stage I and II) comparing "routine follow-up" by physicians compared with "specialist nurse intervention with check-ups on demand." No significant difference in the rate of recurrence was found both in locoregional recurrence and in distant metastases. Survival estimates were similar at 3 and 5 years with event numbers too small to draw conclusions [67].

In a study of 203 patients with resected colon cancers stage Dukes A, B, and C patients were randomized between follow-up by a surgeon and the PCP. In both groups' patients received 3 monthly follow-ups and a yearly fecal occult blood test. Time and number of recurrences were secondary study endpoints after 2 years of follow-up. Recurrence rates were statistically equal, as was time of recurrence detection (with 8 months slightly lower in the surgeon group than the 9.5 months in the PCP group [79]. Again, evidence was of low certainty [80].

Follow-up of colon or early breast cancer, which represents most studies may not allow to generalize conclusions for survival or recurrence in other cancer types.

Other Endpoints

Quality of life, depression, anxiety, and costs have been compared between specialist and PCP FU. In a pooled analysis, there were no significant differences between the approaches with broad confidence intervals and overall low-certainty evidence [80].

Cost-effectiveness has been examined in several settings. The main endpoint for efficiency was the detection of recurrence. PCP-provided FU seeming more cost-efficient as compared to oncologists [81], nurse-led FU seems more cost-efficient than PCP-led FU [82]. Remote FU is even less expensive [83, 84].

Many questions still remain open, as studies with a high level of evidence are still lacking. Many studies have different endpoints and different methodologies of measurement. Shared-care models have not been compared in high evidence studies concerning endpoints.

Current/Existing Models of Survivorship Care

The rising number of cancer survivors and the limited specialist task force have led to progressively consider PCPs for FU [85]. Research has established that while there was no significant difference in outcomes such as overall survival between FU, oncologists, and PCPs have different strengths and weaknesses as well as patient preferences (as pointed out earlier in this chapter). This led to new models of shared care. But the supply of PCP's as a workforce is also ever more limited [86],

and the identified needs of survivors have become more complex. This has brought interest to alternatives such as specialized nurses or PCP's with distinct training. Here are the main current models of survivorship care [87, 88] (Fig. 6.1).

Oncologist-led FU and **PCP-led FU** have already been mentioned earlier. As there is no complex underlying concept, these will not be discussed (again) in detail here. The take-home message is that they have not shown significant differences in randomized studies comparing endpoints such as overall or progression-free survival or quality of life [80]. As already stated, emphasis of oncologist FU rather remains surveillance and detection of treatment sequelae, while PCP FU deals more in depth with non-cancer morbidities, prevention, and psychosocial aspects [89–94].

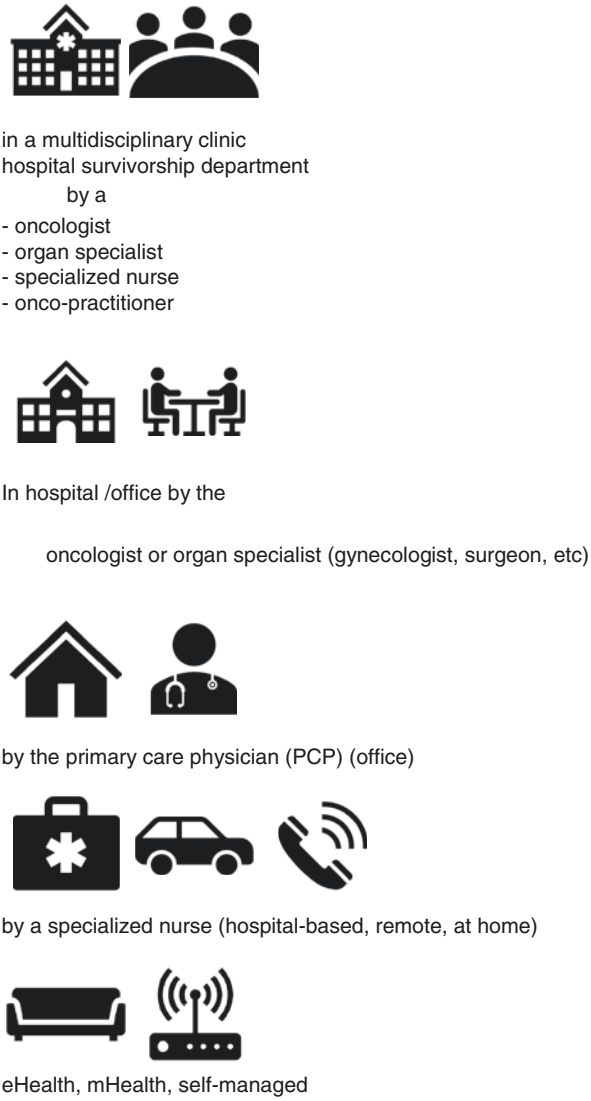

Fig. 6.1 Different forms of FU

Shared Models

Shared-care models are generally well accepted and implemented in a variety of fields of medicine, such as diabetes, renal disease, or anticoagulation [95–97].

The importance of a shared follow-up between oncologists and primary care physicians has been recognized in 2006 with the notion of a transition gap in information and care between the handover from a specialist "back" to the general practitioner, anywhere after the first years of follow-up care after active treatment [1, 2]. There is evidence that cancer patients received less care for non-oncologic matters than healthy controls when treated mainly by an oncologist. Likewise, they (benefitted from more preventive care when treated by PCPs. Elderly patients may particularly benefit from general practitioners' competencies in handling geriatric morbidities [89–94].

The highest possible level of care was provided in a shared-care model. Shared responsibilities also mandated a continuous flow of information between caregivers. Transfer of information between the oncologist and the PCP should be bilateral [1, 89].

Survivors considered oncologists and PCP for different aspects at different timepoints. As fear of recurrence and the need for reassurance play a major role for cancer survivors after completion of active treatment, oncologist FU is favored initially, as they are considered more knowledgeable. Parallel psychosocial support from PCPs is appreciated. Symptom management may be more easily obtained through PCPs between consultations with the oncologist. Within the following years, these issues, as well as concerns in general health bring a shift in the patient's main caregiver towards his PCP, while often after a 5-year follow-up, the role of the oncologist in LTFU fades [1, 49, 62]. There is no sound evidence that shared models provide better overall survival, progression-free survival nor better scores in quality of life and relief of anxiety or depression [80] (Fig. 6.2).

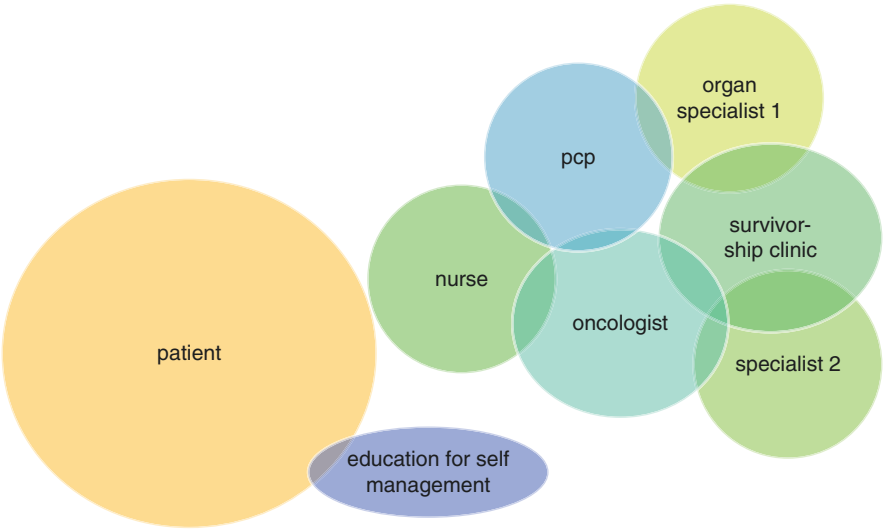

Fig. 6.2 Different actors in survivorship follow-up

Shared Models with Risk-Stratified Individualized Survivorship Follow-Up

Most studies of follow-up care have been made in breast and colorectal cancer survivors. Studies in other cancer types, such as melanoma, seminoma, or non-small cell lung cancer are rare. Risk of recurrence, overall prognosis, and the possibility of life-prolonging interventions do not only vary according to different types of cancer but also on the initial stage of disease, initial treatment, and the general shape of the patient including age, performance status, and comorbidities. Some survivors need complex multidisciplinary management or specific invasive tests in FU, while others only require regular consultations with or without minimal diagnostics. Rare cancers may need highly specialized FU and care in dedicated centers. Identifying the risk of recurrence and secondary malignancies is a major component of survivorship care [98]. Therefore, FU should be tailored individually and shared between oncologists, other specialists, PCPs, or other caregivers. FU frequency and intensity should be based on the patient's risk of recurrence [1, 99, 100], as well as evidence of benefit of a high-intensity approach. The United Kingdom National Survivorship Initiative has already proposed a risk-based FU approach in 2012, implementing all available resources from specialist care to PCP and nurse-led FU as well as remote and patient-empowered self-managed FU [98].

In the classical risk model, survivors are stratified into three risk group models, derived from a depression scale for primary care. The risk group defines whether survivors will be followed-up primarily by oncologists, PCP, or both and to what intensity [101].

According to stratification,

- Low-risk survivors have common cancers (breast, colorectal, prostate) in early stage, and receive standard treatment. These patients are directed for main FU to the PCP, in particular in presence of high non-malignant comorbidities.
- High-risk cancer survivors have rare cancers or more advanced stages of malignant disease, complex treatments with high risk of late and long-term effects. These are considered to require integrated constant specialist FU care (including the option of an "onco-generalist") in a shared model.
- Intermediate risk survivors have fewer common cancers or rather advanced stages, multimodal treatments, and a moderate non-cancer chronic condition burden. These patients may require more expertise than provided by regular PCPs suggesting specially trained general practitioners ("onco-generalists") or management in clinics. As an alternative, these patients might benefit from FU by caregivers in a survivorship clinic-like structure [49, 98, 99].

Nurse Practitioners in FU

Specialized nurses are increasingly commissioned for follow-up of cancer survivors. Models range from consultations in a (hospital-based) survivorship clinic to home visits and telephone-based FU [102–110]. In the United Kingdom, Canada,

and other countries, nurse practitioners (NPs) or specialized nurses are primarily responsible for hospital follow-up. This means that the patient has to visit the nurse for consultation in the hospitals [102, 103]. Other, more recent models include telephone-based consultations or even home visits [107]. Nurse-led FU has been reported to be safe and equivalent to physician-led FU in study endpoints such as survival, recurrence detection, quality of life, or patient satisfaction [104–110]. Patients seem highly satisfied with nurse-led FU as nurses "were easier to talk to and had more time." They were described as being accessible, had a personalized approach, and were attentive towards psychosocial needs. The lack of specialist knowledge and skills was addressed as a disadvantage of nurse-led follow-up [57, 70, 101].

Telephone-based care has proven to be a feasible alternative to traditional clinical FU. This may be especially advantageous for older and frail patients with comorbidities and difficulties leaving their home for hospital visits. Since it does not require face-to-face visits, patients need less traveling time and efforts as well as less expenses. In the literature, telephone-based follow-up is most commonly carried out by nurses [108–112].

Virtual Follow-Up

More recently, video-assisted consultations via smartphone or personal computer [113–118] have emerged. Video consultations (VC) offer the advantages of telephone-based consultations in terms of costs, patient's efforts to present at the hospital. As compared to telephone consultations, they may be particularly interesting when visual diagnostic decision-making is of interest [114]. Also, in case where emotions need to be better captured—both in the case of delivery of good news as well as bad news. In comparison, VC provided higher diagnostic accuracy, less medication errors, and better decision-making when compared with telephone consultations alone [114, 116].

eHealth and eMedicine in Survivorship Care FU

The rapidly evolving communication technologies and ever broader use of computers, tablets smartphones, and other devices as well as the explosion in the development of applications broadly used all over the globe have continued to give rise to ever newer and more perfectioned forms of telecommunications, live as well as through automated algorithms, in every aspect of everyday life, including medicine, in forms of eHealth and mHealth [119, 120]. In the following I will use the following definitions:

"eHealth" refers to the broad use of health information and communication technologies and networks to enhance patient-centered care delivery. Other terms commonly used interchangeably with eHealth include telehealth, telemedicine, and teleoncology.

"mHealth" refers to the use of mobile and wireless devices (e.g., computers, tablets, and smartphones) with health applications that support patient care, education, and research. We also include health information technologies, which refer to technologies that support the collection, aggregation, and management of health information (e.g., electronic health records and online portals) [119].

eHealth and mHealth shift the primary intention from the caregiver (oncologist, PCP, nurse, etc.) towards the patient himself.

Applications are multiple: eHealth and mHealth technologies are "home-based" and allow access to survivorship care in remote areas or for patients with physical disabilities or frailty, which make institution-based consultations difficult. A major advantage is to provide rapid access to specialized care in this survivorship population [118]. Other strengths are efficient connection within treatment networks and patients [120, 121], symptom control, establishment of individualized survivorship care plans, and patient education [119].

eHealdh and mHealth greatly facilitate documenting and treating patient-related outcomes (PRO) which are increasingly recognized as essential in the supportive FU of cancer patient during treatment [122–124]. PRO provide information deriving directly from patients without interpretation or amendment from caregivers thus avoiding the risk of underreporting and under-recognition by caregivers [122]. eHealth devices may enhance collection of PROs, spread communication among multidisciplinary teams in real-time, and even permit patient self-management through decisional algorithms. Their implementation in survivorship is raising increasing interest and is subject to various ongoing research projects [119, 125]. Telemedicine interventions are generally well accepted by patients and highly cost-efficient [126, 127]. They are also advantageous since they are easily deployable in countries and areas with low population density or/and limited resources [128, 129]. Remote surveillance programs using on-demand consultations, emails, and video-conferences in the FU of genito-urinary and breast cancers in the UK and Canada have been shown to be safe with comparable outcomes, less costly, and favored by patients [126, 130].

Remote patient management through eHealth and mHealth have gained recently an even higher importance as they allow increased patient's safety during the COVID19 pandemic [131].

eHealth and mHealth technologies may alleviate pressure from overloaded caregivers through patient empowerment and increased self-management [125]. Artificial intelligence and more sophisticated algorithms may provide survivorship care in a more pluri-dimensional, individualized, and holistic approach: "What works for whom in which circumstances?" [132, 133].

Though highly promising, high-level evidence of benefits and comparisons with other models are still often lacking. Implementation within an already busy workflow for caregivers, universality in use for all patients, and compliance are issues.

Age, patient education, medical literacy, and access to the Internet are major determinants for the implementation and use of eHealth and mHealth in cancer [134, 135].

Patient Self-Management

60–90% of recurrences are detected by the patients themselves in between regular follow-up visits [136, 137]. Evidence of a measurable benefit in survival, early diagnosis of recurrence is lacking for many surveillance models. The traditional form of regular face-to-face FU consultations with test prescription for surveillance has also been challenged in this context, as patient empowerment through education and patient-centered access to care are becoming increasingly available through eHealth and mHealth [138–140].

In consequence, a further alternative to traditional FU is patient empowerment and self-managed FU care, mainly supported with remote and virtual tools [125, 141]. Self-management and self-referral with the aid of survivorship care plans are even more seducing concepts in the face of shortages of the oncologic workforce. Patient care can be provided through telephone FU or technology-aided FU through applications, video consultations, e-mailing, or their combination [119, 125].

Patient empowerment through education and intensified contacts, either by phone or electronically have been compared in numerous settings. Studies integrating symptom education and monitoring varied in methodology and endpoints (which did not include overall survival or early recurrence detection). There is so far no proven and confirmed advantage of this intensified approach over usual FU care [80]. A shift towards more self-management seems however a logical consequence of the ever more limited resources of specialized caregivers and individualized patient care. Therefore, superiority as compared with a control group might not be a necessary endpoint to favor these approaches. In fact, self-managed FU care seems at least equivalent as compared with traditional FU in some studies. Patient-led and self-managed FU has been shown to be well accepted, cost-efficient, and comparable in safety and guidelines compliance in various studies, at least in a low-risk population [142–145]. Self-management and empowerment need guidance and support to succeed, raising the importance of survivorship plans [146]. Telemedicine has greatly advanced self-management strategies [88, 116].

Europe and Survivorship Care

The United States Commission on Cancer has established a framework defining standards in survivorship care for patients treated in curative intent for stages I–III, who have completed active therapy (other than long-term hormonal treatment). Its implementation is mandatory for accreditation as a recognized cancer center [147]. Unfortunately, effective survivorship care is highly heterogenous in its availability and form throughout Europe. Survivorship programs, whenever present, are mainly established by individual institutions, rather than nationwide or on a regional level. Healthcare providers and systems vary with different available workforce resources, health service providers, and budgets, differently defined responsibilities among caregivers and reimbursement schemes. There are multiple stakeholders involved in

survivorship care issues. Distance and access to care may differ greatly for patients depending on their geographic location [148].

Past and present initiatives on national and European levels tend to provide equal access to survivorship care to patients across Europe [149–152].

Conclusion

Ever since survivorship care was identified as a major need for cancer patients after active treatment by the Institute of Medicine and the call for a structured approach [1, 2], the definition of its contents and the involved caregivers has changed and diversified over time in parallel both due to caregiver's and patients' perceptions and needs.

As a limited workforce encounters ever more cancer survivors living longer, the traditional model of specialist follow-up, derived from pediatric oncology FU, is unsustainable. Thus, responsibilities for surveillance have been progressively shifted from specialists to general practitioners, nurses, or other caregivers. This has generally been proven to be safe, with certain advantages and disadvantages linked to each model (expert knowledge, prevention, comorbidities, etc.). Lately, eHealth and mHealth provide even further tools to rationalize workforce and expenses while providing more intensive follow-up options with high patient satisfaction.

As cancer survivors live longer, their needs also change over time: The concern for recurrence diminishes, comorbidities may increase—and some sequelae or risks of treatment-related late effects last. This has led to the appraisal of shared models between specialists and general practitioners or other caregivers.

At the same time, ever more complex needs have been identified in cancer survivors, which vary according to cancer type, stage, and comorbidities, but most of all to the individual patient. These are also increasingly identified and listed by patients themselves, who aim at more empowerment and participation in management issues. Comparably to active treatment, survivorship care has evolved—at least in theory in personalized medicine with individualized care.

As follow-up care has gradually evolved from pure surveillance to survivorship care, holistic management clearly requires a multidisciplinary approach which has to accompany patients in their everyday life. This can only be provided by a multidisciplinary team and needs continuous access rather than cumbersome convocations within lengthy intervals.

So, who should be the provider for follow-up care? Most probably, many different models exist and can be considered. In a heterogenous landscape, it may very well be a different person or setting in one country, region, or institution than in another. For some, treatment-intense and complex types of cancer, such as head and neck cancers, the general FU considerations are insufficient: multidisciplinary and specific survivorship FU has to be planned [153].

Today, we define far better the needs of our patients in survivorship care, and—our empowered patients wish increasingly to actively participate in their care management, also articulating far better their needs. Taking into account the evidence

stated in this chapter, it seems to the author, that the best model for the individual patient will be the one which realistically best covers his needs in his environment.

This implies a well-managed transition from active treatment to survivorship care with clearly defined tasks for the participating caregiver(s) and one identified "key contact" person [154]. One proposed method to achieve this is a survivorship plan [2].

CanCon resumes as follows

- GPs or a primary care team should play a relevant role in patients' follow-up;
- the follow-up model should provide a rapid reentry to specialized cancer care, if required; and
- a health care professional should assume the role of a coordinating case manager by being a point of reference and contact for the patient and the team [155].

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7 Identifying the Cancer Survivors' Needs in Daily Practice: Do we Have a (Survivorship) Plan?

Stefan Rauh

The Survivorship Plan

In 2006, the Institute of Medicine (IoM) identified essential items for cancer patients to be included in every cancer patient's follow-up care [1].

According to the IoM, the issues for cancer survivors to be covered are: [1]
1. Prevention of recurrent and subsequent primary cancers, and of other late effects.
2. Surveillance for cancer spread, recurrence, or secondary cancers.
3. Assessment of medical and psychosocial late effects.
4. Intervention for consequences of cancer and its treatment, for example, medical problems such as lymphedema and sexual dysfunction; symptoms, including pain and fatigue; and psychological distress experienced by cancer survivors and their caregivers.
5. Evaluation of concerns related to employment, insurance, and disability.
6. Coordination between specialists and primary care providers to ensure that all of the survivor's health needs are met.

As patients move from often busy treatment schedules to surveillance, they hope to return rapidly to a "normal" life. They may experience an abrupt loss of contact with their former caregiver, mostly an oncologist. Symptoms due to sequelae or treatment side effects may however prevail, new morbidities may emerge. Unprepared patients often lack tools to help them evaluate symptoms for seriousness and need for management. This leads to increased emergency department visits, a high level of uncertainty, anxiety, and a loss of quality of life [2–5].

Primary care physicians (PCP) may not provide adequate expert knowledge of recurrence risks and treatment-related late effects, whereas specialists may underrecognize and treat non-cancerous pathologies [2, 6, 7].

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The IoM described the challenge of transition from active treatment to follow-up, with a need for sharing coordinated care between caregivers, defining endpoints, and empowering patients for self-management.

A main tool proposed to achieve these goals was a **"survivorship care plan"** (SCP) which was to be established for every patient at the end of active treatment and delivered to him as well as his PCP [1].

Its first intention was to present a framework for follow-up (FU) and allow a primary care practitioner (PCP) to receive the necessary information to take over the patient's care so as not to be "lost in transition." It also emphasized that patients' needs were far beyond surveillance [1]. In the meantime, SCP has become a standard recommendation in the United States, also as requisite for accreditation of comprehensive cancer centers [8], as well as for reimbursement by MedicAid and MediCare programs [9].

SCPs have also been proposed by expert groups in Europe. "Cancer Control Joint Action" (CanCon) stated the low added value of standard surveillance in current practice, the frequent disregard of multidisciplinary teams concerning rehabilitation and survivorship issues, and a lack of vision of both endpoints and distribution of responsibilities among caregivers. CanCon considers a specialist, part of the initial multidisciplinary team, as initiator to establish a survivorship plan to create a holistic and integrated approach to survivors' health. SCP in this definition means primarily to define needs, plan and organize a framework for FU with all involved caregivers and stakeholders. Distributing necessary information on past treatments and proposed follow-up to the patient and the PCP is a second aim (survivorship passport, see below). As health systems vary among Europe's member countries, CanCon proposes essential conditions in the establishment of a SCP:

- a relevant role for the PCP/team,
- rapid reentry to specialist care, when necessary,
- the provision of a designated health professional taking the lead as coordinator, referent, and contact person for both patient and multidisciplinary team,
- patients should be provided relevant information on late effects of the cancer treatments received, and have them readily available for all (future) caregivers, possibly in form of a "survivorship passport."

There is no uniform approach to the organization of survivorship care in Europe [10]. In a study, only a subset of 36 European countries provided guidelines for major tumor types, with survivor care in even less (mainly for breast cancer). Overall, "after-care guidelines" focused mainly on screening interventions for recurrence, while (apart from breast cancer) there was little emphasis on preventive measures, late effects symptom control, or psychological issues. SCPs seemed to be absent [11].

When Should a SCP Be Made?

A survivorship plan should be considered like a hospital discharge letter [7, 12]. Patients seem to have a clear preference for receiving a plan defining future steps in surveillance and prevention before or at the end of active treatment [12, 13].

What Should a SCP Include?

According to the NCCN guidelines, a cancer survivor follow-up plan should include the following elements [14]:
1. Information on treatment received including all surgeries, radiation therapy, and systemic therapies
2. Information regarding follow-up care, surveillance, and screening recommendations
3. Information on posttreatment needs, including information regarding acute, late and long-term treatment-related effects, and health risks when possible
4. Delineation regarding roles of oncologists, PCPs, and subspecialty care physicians in long-term care and timing of transfer of care if appropriate
5. Healthy behavior recommendations
6. Periodic assessment of ongoing needs and identification of appropriate resources

Who Should Establish the SCP?

It will mostly be the oncologist or other specialist for the active treatment who will establish the survivorship care plan. Due to time constraints, this is however a barrier to its implementation. Other models have included nurses, research assistants, or PCPs as SCP editors with satisfactory results [15].

Who Should the SCP Be Addressed to?

Mainly intended to provide necessary information during transition from specialist to the PCP, SCPs have considerably evolved towards patient education and empowerment. Therefore, a SCP should provide information to both the patient himself as well as the caregiver who will take over—or share—the patient's follow-up [12].

What Would Be the "Ideal" SCP According to Patients?

According to a survey among patients and PCP concerning preferences of SCP, these were the results:

- Easy-to-read format and language.
- Important contact information of providers (whom to call for what problems and how) on the front page.

- Diagnosis and disease stage.
- Current disease status (remission, residual disease).
- A treatment plan with purpose (control, palliation, cure) in understandable language.
- Listing of complications or ongoing problems.
- Suggested questions to ask the care provider.
- Information on health promotion including nutrition and physical activity.
- Description of what recurrence looks like, knowledge on what to report, and what not to worry about.
- Listing of local resources (financial and social support, transportation, community resources).
- Area to write "I have concerns" [16]

Patients wished to receive their SCP at the end of treatment, but not the last day, as a (written/printed or electronic) document during a meeting with their principal care provider. They would use it as well as support for consultation with their future caregiver(s) as well as with family members or friends. Some would just use it as a back-up document [16]. Patients varied in their request for details and contents, with a tendency towards a more detailed document [17].

PCP had Similar Preferences, Detailing

- An easy-to-read format with no more than 2–3 pages.
- Frontpage with contact details of oncology providers.
- Diagnosis and disease stage.
- Treatment delivered in understandable language, not too detailed.
- List of complications and unsolved problems.
- Potential long term and late effects [16]
- Distribution of a document was however not sufficient for implementation and patient satisfaction, which varied among patients and required individual approaches as well as educational efforts. These findings concurred with other studies concerning SCP [16–20].

Existing Templates

SCP templates exist since a number of years in the United States, provided by Livestrong, Oncolink, Journey Forward, and the American Society of Clinical Oncology (ASCO) [21]. In Europe, the European Society of Medical Oncology (ESMO) and the European Cancer Patient Coalition (ECPC) have proposed a first general survivorship guide with SCP template in 2017 [22].

Are SCP Implemented?

SCP are highly welcomed by patients and PCP [16]. They are an integral part of current quality accreditation programs in the United States. It may thus be surprising that SCP are far less implemented than expected [17, 23, 24], and that their routine use is mainly restricted to breast and colon cancer patients also depending on caregivers, institution, patient education, and regional infrastructure [24, 25]. The least chance to benefit from a SCP seems to be in a community oncology setting [25].

Establishing a SCP is time and resources consuming (estimated at 90–120 min per patient), which is a major burden considering the available workforce and may block valuable resources. Further work and time may be necessary in the absence of an efficient electronic data collection system and the need to complete the SCP after searching and collecting missing documents. Lacking reimbursement is another barrier [25]. In principle, SCPs should be provided for each tumor type and possibly stage. Differences in patient education and their willingness for empowerment and management sharing lead to different needs of SCP contents and educational efforts to make them understandable and useful.

Evidence of Benefit of SCP

There is currently still (?) a lack of evidence of the benefit of SCP as compared to standard FU in cancer survivors, which is another barrier for their implementation. There is neither evidence of a survival benefit nor benefit in another stringent endpoint [26]. In a meta-analysis comparing eight studies with 1286 patients and a combined systematic review in 18,949 survivors, there was also no evidence on patient-related outcomes such as anxiety, depression, physical function nor with information provision or self-efficacy. According to the same study, SCP may however improve patients' adherence to medical recommendations and improve knowledge of health care providers in survivorship care and late effects [27]. These seemingly contradictory results may be due to the heterogeneity and lack of sufficient statistical power of the existing studies. It may also be due to poor compliance or lack of adherence. This might be a consequence of inadequate training and support to both patients and caregivers [27–29]. In the absence of clear evidence of stronger endpoints, there remains evidence of high patient satisfaction and evident "face value" [1, 15].

Conclusion: Plan your Life—Live your Plan?

It seems common sense to establish a clear plan of the needs of cancer survivors both in terms of surveillance and support, attribute responsibilities and provide a document with all indications to the patient and the PCP or other caregivers, either in print or electronically. In practice, several barriers have hampered this effort,

which may further be questioned due to the lack of evidence of significant benefit in existing studies.

Patients' wish to receive guidance, references easy to contact, and a structured reassuring should not be underestimated. Neither should be the PCPs' need for clear information. Efforts should be made to provide more patients with guideline-based survivorship care plans which should reflect the patients' local conditions rather than a European uniform model.

What Should Follow-up Visits Include?

Follow-up visits are proposed in a regular fashion, ranging from trimestral to yearly intervals.

In addition to screening by history and physical examination, care providers should (re) assess the following at regular intervals [13]:

1. Current disease status.
2. Functional/performance status.
3. Medication use (including over-the-counter medications and supplements).
4. Comorbidities.
5. Prior cancer treatment history and modalities used.
6. Family history.
7. Psychosocial factors.
8. Weight and health behaviors that can modify cancer and comorbidity risk (including cigarette/tobacco, alcohol use).
9. Disease-specific recommendations for surveillance/follow-up.

Detecting Distress, Anxiety, and Depression

Distress has many definitions (see, for example, various dictionaries), and may be used synonymously with great pain, anxiety, or sorrow; acute physical or mental suffering [30].

Most definitions characterize distress as an aversive, negative state in which coping and adaptation processes fail to return an organism to physiological and/or psychological homeostasis [31].

The NCCN defines distress as follows:

"Distress is a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual, and/or physical nature that may interfere with one's ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis." [32].

Distress with anxiety and depression are present in a high number of cancer patients, mostly related to the fear of recurrence. Between 14% and 56% of patients will face these symptoms in various degrees after diagnosis [33, 34]. Understandably, these conditions negatively influence quality of life, and may even lead to suicide in some patients [35–37]. They may also negatively influence the patient's compliance with surveillance and treatment, and provide barriers for reintegration and rehabilitation efforts, as well as to the persistence of unhealthy lifestyle habits [35]. While anxiety and depression peak at cancer diagnosis, they do not necessarily cede at the end of active treatment but may stay on a plateau level or even slightly rise [38, 39]. This is amplified by the sudden drop in the frequency of consultation visits at the transition from the busy treatment schedule to infrequent FU visits [26]. Anxiety and depression may gradually decrease but prevail for over 10 years for many cancer survivors, and never cede in a minority of these [39].

Anxiety and depression are still highly underreported and remain unrecognized during busy FU visits. Referral for psychological and psychiatric support are especially low in oncologic community settings [40, 41]. This is all the more unacceptable as psycho-oncologic interventions have a proven benefit in clinical studies [42].

The use of tools to detect distress is highly encouraged. NCCN provides a "distress thermometer" as a simple visual tool, enabling patients to score levels of distress between 0 (cool, no distress) and 10 (boiling, extreme distress), with a cut-off score of 4 and higher triggering identification of the problem with a corresponding "problem list" for patients to check and forward to their caregiver during visits [32]. This tool has been validated in a series of studies in various languages and countries with high sensitivity and satisfying specificity [43–46]. It can be downloaded from NCCN's website [47].

Is Intensive FU Better than Non-intensive FU?

There is considerable debate over the usefulness of more or less intensive FU, both in terms of surveillance and detection of recurrence, as concerning patients' needs, anxiety, and distress. Comparisons in stage I–III colorectal cancer patients came to different results in terms of overall survival. Some studies show modest but significant overall survival gains (without cancer-specific overall survival) [48, 49], while others did not find any significant overall survival advantage [50, 51]. However, there seems to be converging evidence of better early detection of early recurrence with more "intensive" FU, as analyzed in a Cochrane review of follow-up strategies: Selected studies in breast, colon, lung, and other cancers showed overall survival advantages, the meta-analysis a trend in favor of intensive follow-up, with low-certainty evidence. Early detection of recurrence was significantly better with a hazard ratio of 0.85, a confidence interval of 0.79–0.92, and a p-value <0.0001 [26]. The lack of a meaningful survival advantage may be due to lack of statistical power of the studies, but also of the underlying disease and the available treatment options in case of relapse.

As an example, intensive FU has not provided a significant survival benefit in breast cancer. A detrimental effect has even been reported (maybe due to toxic treatments being deployed earlier than needed) [52]. In breast cancer, recurrence in terms of metastatic disease will nearly always remain incurable, independent of early or later detection. The main determinant for the patients' prognosis will therefore rather be his performance status and general shape (so as not to jeopardize the best available treatment), and the absence of vital complications arising from the metastatic spread [52–54].

More intensive FU also shows controversial results in potentially induced raised anxiety and distress, probably also reflecting that some cancer survivors will be reassured, while others distressed anticipating the upcoming visits, while still others will not be affected [5].

In conclusion, the author of this chapter believes that evidence and lack of evidence concerning the intensity of FU should be discussed between caregiver and the individual patient, as well as "side effects" such as anxiety or distress. Some patients may prefer more intensive FU, while others less often or an "on demand" model. A consensual schedule including frequency and tests should be "negotiated," documented and applied. A framework of currently suggested surveillance is delivered in another chapter of this book.

Multimodality: Leaving the Landscape of Regularly Scheduled FU Visits

eHealth, the use of electronic information and communication technologies in medicine to enhance patient-centered care has already been mentioned in the previous chapter. Recent years have seen an impressive proliferation and broadening of eHealth interventions [55], as both hardware and software evolve with ever higher speed, and as these technologies are continuously integrated into a higher and higher proportion of our daily lives.

eHealth has shown high potential in raising health-related quality of life and symptom burden in cancer patients. In survivorship care, eHealth enables easy and real-time collection of patient-related outcomes (PRO), which have been shown to enhance patient-physician communication, raise awareness of symptoms, and thus avoid the risk of under-reporting in physician-reported conditions. It also provides an easy connection of the patient with his caretakers, without the need to leave home, which is of particular interest for frail patients and patients living remotely from their care provider(s). Artificial intelligence allows more and more complex and multimodal approaches with minimal costs and time constraints [56, 57]. eHealth is however also a vast and heterogenous area with a broad range of different hardware and software, different measured points, methodologies, and—in studies—different settings and endpoints which make comparisons as difficult as the choice of the best standard. Its rapid evolution makes it even more difficult to settle on a standard approach.

The implementation of eHealth has been accelerated since the beginning of the COVID pandemic [58]. In terms of symptom control, there is data in favor of better self-management and a decrease of pain conditions [59, 60], decreased fatigue [61], and lesser distress [62] in some studies comparing eHealth interventions with standard care. A Cochrane review of home-based multimodality survivorship programs found a short-term significant benefit in quality of life and which was related to the reduction of anxiety, fatigue, and insomnia directly after the intervention [63].

The true value of electronic systems for patient reports and symptom control remains however unclear and controversial. Many studies and systems provided neither an interaction means between patients and caregivers, nor between patients; others did not enable patients to monitor their symptoms or did not provide means for self-management, even though these features have been identified as highly valued [55]. Even when these features were combined in a sophisticated eHealth application, main endpoints such as the amount of knowledge, skills, and confidence for self-management and health-related quality of life were not significantly improved [63].

eHealth interventions are generally well accepted by patients, without major differences on behalf of patients' education [64, 65]. Age is (still) an issue, as older patients may feel less comfortable with the use of Internet- or smartphone-based interactive resources [66]. Patient compliance is an issue, as patients need to keep motivated to use their device or program to keep it functional. Patients may abandon due to lack of motivation, or to the monotony of repeatedly asked questions [67]. Different personality profiles may play a role: patients with limited "self-efficacy," who need to be encouraged, motivated, and led may profit more than others from stimulating programs, while fully automated and self-managed applications may give highest satisfaction to patients with high medical literacy and a high level of personal autonomy [68]. On the caregiver's side, their implementation is hampered by the potentially higher caregivers' workload, overload of provided information, and lack of motivation [69].

In conclusion, eHealth should be integrated into SCP and FU models without further burdening the workload of caregivers, and adaptable to tailoring for different profiles of patients. Research efforts trying to detect means to obtain major benefits and adherence are ongoing.

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8 Follow-Up after Cancer Treatment—Evidence Gaps and Trends in Survivorship Care

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Approximately 19 million people worldwide are diagnosed with cancer each year and this number is projected to rise in the coming decades due to longer lifespans and our modern lifestyles [1]. At the same time, survival rates have continually improved. Over the past 40 years, overall 5-year survival rates have increased from about 50% to almost 70%, meaning that two-thirds of all cancer patients today will become long-time survivors [2, 3]. The simultaneous increase in both cancer incidence and survival has led to a burgeoning population of cancer survivors, which has been dubbed the "survivorship tsunami" [4]. This makes issues of survivorship increasingly important to a larger and larger section of the world's population. Thus, one of the biggest challenges facing the practice of oncology today is how to

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provide safe, effective, and economically sustainable follow-up care to this growing group of survivors.

What is Cancer Follow-Up Care?

Traditionally, the main aim of follow-up has been to detect a possible recurrence (or new primary cancer) after the primary treatment has ended so that prompt treatment may be initiated to improve prognosis and survival [5]. While cancer follow-up is currently an important area of oncology research, the practice originated in large part *due* to research in the 1960s and 1970s, as surgeons and oncologists in the United States and Europe carried out many trials testing different treatment protocols across cancer sites [6]. After completion of treatment, patients were followed over time and each follow-up visit without a relapse in the patient provided evidence supporting the effectiveness of the protocol.

Thus, for decades, the traditional model of follow-up care has consisted of fixed appointments consisting of physical examinations and/or diagnostic tests with a physician [5, 7]. Follow-up visits are usually more frequent (e.g., every 3 months) during the first few years posttreatment, where the risk of recurrence is highest and becomes less frequent later (e.g., once a year) [8, 9]. This schedule is based on the assumption that early detection of recurrence is important for improving survival through the prompt initiation of treatment [10]. Follow-up visits are also important to many patients, as they provide reassurance that a potential relapse will be detected and help patients transition from the close medical care that they received during active treatment [11].

The Challenges of Traditional Follow-up Models

Efforts to rethink follow-up care began in the 1980s as survival rates improved and it became apparent that the constrained resources of national healthcare systems would not be able to sustain a follow-up model based on specialist-led visits and expensive diagnostic tests [12, 13]. A second driver was the emerging research that questioned the effectiveness of routine follow-up procedures and whether they provided any survival benefit compared to, for example, less intensive schedules [5, 12]. Finally, the traditional focus of cancer follow-up on early recurrence detection was becoming insufficient, as survivors began reporting many unmet needs stemming from the long-term physical and psychosocial sequelae of having cancer [14]. Cancer was becoming a chronic condition for more and more survivors and new ways of meeting their needs were needed [15]. Thus, researchers began developing and testing alternative follow-up models, whereby components of the traditional follow-up model were changed or new components were added. Subsequently, focus on late-effects and quality of life for the cancer survivor is increasingly recognized as an important element in current follow-up care [16, 17].

Alternative Follow-up Models

In order to study the different follow-up models, one framework that has been used to systematically distinguish between the various components in newer approaches is the why, who, what, where, when, and how framework [9]. In Table 8.1, we give examples of the different components of traditional and alternative follow-up care models according to this framework. From the table, it is clear that follow-up care has become very complex with multiple aims such as improving survival, recurrence detection and quality of life.

The Evidence for Different Follow-up Models

The earliest published randomized trials comparing different cancer follow-up models were carried out in Italy by the GIVIO group [18] and by Rosselli Del Turco et al. [19]. Results from these two trials were published in JAMA in 1994 and showed that follow-up after breast cancer with the addition of chest x-ray, bone scintigraphy, liver echography, and blood samples to regular appointments and mammography did not improve survival, although one of the studies found a

Table 8.1 Examples of the different components of traditional and alternative follow-up care models

	Traditional follow-up model	Alternative follow-up models
Why cancer follow-up?	• Early detection of recurrence or new primary cancer to improve survival	• Early detection of recurrence or new primary cancer to improve survival • Provide surveillance and management of side-effects and late-effects to improve quality of life
Who provides follow-up care?	• Specialists (e.g., oncologists or surgeons)	• General practitioners • Nurses • Specialists when needed
What is delivered?	• Anamnestic history • Physical examination • Diagnostic tests	• Anamnestic history • Physical examination • Less or more intensive diagnostic tests • Patient education to improve self-management skills • Survivorship care plans • Navigation to rehabilitation services
Where is follow-up care delivered?	• Hospital	• Hospital • GP office • Patient's own home
When is follow-up care delivered?	• Fixed calendar-based appointments	• Fixed calendar-based appointments • Needs-based (patient-initiated)
How is follow-up care delivered?	• Face-to-face appointments	• Face-to-face appointments • Telephone or web-based

reduced time to detection of recurrence with the additional diagnostic tests [19]. The GIVIO study also demonstrated no difference in the quality of life depending on the intensity of follow-up [18]. Results from the third trial by Grunfeld et al. were published in the BMJ in 1996 and showed that follow-up after breast cancer led by general practitioners (GP) in primary care might be just as effective as specialist-led hospital follow-up with regards to time between first presentation of symptoms to confirmation of recurrence and quality of life [20].

These pioneering studies were among the first to show that cancer follow-up could be delivered and organized in alternative ways that were potentially safe and cheaper than traditional follow-up. For patients, fewer or less invasive tests may mean less burden and some may find it easier to contact their GP or a nurse for advice compared to a specialist.

All three of the abovementioned trials were carried out in the breast cancer population. However, over the following decades, more and more trials were carried out testing a wider range of alternative follow-up models in multiple cancer sites. As the number of trials increased, systematic reviews were published to synthesize the evidence from these trials. Below, we give a brief overview of the evidence from the available systematic reviews regarding the effectiveness of follow-up models led by GPs and nurses and by follow-up models based on less intensive or fewer components such as diagnostic tests and visits.

Can GPs and Nurses Safely Take over Follow-Up Care?

GP-Led Follow-Up

Since the pioneering study published by Grunfeld and colleagues in 1996, very few randomized trials have been carried out comparing GP-led follow-up in primary care to conventional hospital-based follow-up. The latest systematic review examining cancer follow-up in primary care versus secondary care identified seven publications from only five randomized trials, while the remaining nine studies were observational [21].

Due to the heterogeneity of the studies, no meta-analysis was carried out, but based on all the included studies, this review concluded that no important differences were seen in the outcomes survival, number of detected recurrences or progression, overall quality of life, anxiety, and depression [21]. The results also showed that GP-led follow-up was associated with a lower cost to patients and society [21]. High levels of patient satisfaction and perception of care were reported for both GP and hospital-based follow-up, but a few studies found that patients preferred hospital-based follow-up, as they were reassured by access to specialist care and felt that GPs lacked specialist knowledge [21]. Thus, although GP-led follow-up appears feasible and potentially cost-saving, the evidence that it is just as safe and acceptable for patients compared to conventional follow-up is not strong due to the few studies available and the lack of power in these studies for assessing outcomes such as survival.

Nurse-Led Follow-Up

In order to diminish resource utilization and enhance continuity of care, it has been investigated whether nurse-led follow-up is equivalent or even superior and more cost-efficient compared to traditional follow-up. In a recent Cochrane review covering different follow-up strategies among cancer survivors across adult cancer types, six studies investigating nurse-led versus physician-led follow-up were identified [9]. Of these six studies, none were powered to identify differences in time to detection of recurrence or survival. Overall, these studies reported no significant differences in quality of life, anxiety, or depression in nurse-led versus specialist-led follow-up [22–27], whereas two studies reported improved patient satisfaction with nurse-led follow-up [22, 23], and two studies found no difference in satisfaction with care [24, 27]. The evidence on cost is inconclusive as three studies reported lower costs per patient followed in a nurse-led program, whereas two studies came to the opposite result [9].

Finally, a systematic review of nurse-delivered cancer survivorship care demonstrated benefits on cognitive and social functioning but not on other quality of life domains, which is in line with the findings from the Cochrane review above [28]. The interventions in the included studies frequently combined the nurse-delivery with additional patient assessment, clinical management of problems, patient education, individualized care, and supported self-management [28]. Thus, the lack of a significant positive effect on the patient's psychological well-being and quality of life is surprising and indicates that we still lack knowledge on how to improve and adequately assess these aspects of survivorship care. In conclusion, nurse-led follow-up appears feasible and it is probably equal to specialist-led follow-up in terms of supporting quality of life and reducing anxiety and depression in the patients, but whether it equals specialist-led follow-up in terms of survival and recurrence detection is yet to be established.

Can Patients Safely be Followed up with less Intensive Strategies?

The best-investigated aspect of cancer follow-up has been whether the intensity of diagnostic tests makes a difference in survival and recurrence detection [9]. Intensity may be defined by the type of test itself (e.g., x-rays are considered a less intensive test than a CT scan) or by the frequency of the test (e.g., an annual colonoscopy would be considered less intensive than having a colonoscopy every 3 months). Again, the evidence mostly comes from breast cancer and colorectal cancer.

For breast cancer, the results have been fairly consistent in showing that less intensive follow-up (physical examination and annual mammography) does not worsen overall survival compared to more intensive follow-up including frequent tests such as chest x-rays, bone scintigraphy, and blood tests [7, 29, 30], although newer studies with more modern imaging techniques are warranted [16]. However, for colorectal cancer, systematic reviews have differed in their conclusions

regarding the two types of follow-up, with some reporting no difference in survival and detection of recurrence [10, 31] and others reporting that more intensive follow-up improves survival and detection of recurrence [32–35]. This divergence may be due to the different included studies, and how the outcomes are measured and meta-analyzed.

However, a more important factor may be the fact that diagnostic tests and cancer treatments continue to change and improve, and the inclusion of new trials can change the evidence. Some of the current guidelines may be based on outdated evidence. Follow-up guidelines for breast cancer, for example, are still largely based on the two landmark trials in Italy, recruiting patients in the late 1980s [16, 36]. Diagnostic imaging has improved since then and newer treatment modalities have increased survival markedly, even for advanced-stage breast cancer. It is possible that more frequent and intensive tests today may identify breast cancer recurrence at a much earlier stage, where more effective treatment may lead to survival benefits. The ongoing KRONOS trial in Italy testing a more intensive follow-up program based on CEA and CA15-3 evaluations, as well as 18-FDG PET scans in breast cancer patients, may be expected to provide updated evidence for breast cancer follow-up [37, 38].

Until then, the largest meta-analyses across cancer sites indicate that less intensive follow-up may make no difference in overall survival, but may delay the detection of recurrence when compared to more intensive follow-up [9]. However, since the included studies did not analyze survival according to time to detection of recurrence, no conclusions can be made about the role of early detection of recurrence on overall survival [9]. Interestingly, very few of the available trials investigated outcomes such as quality of life, anxiety, and depression. Thus, we still know very little about how intensity of tests and appointments affects the well-being and quality of life of cancer survivors, which is an important knowledge gap.

Trends in Current and Future Survivorship Care

Besides research investigating the optimal provider of follow-up (specialist-led vs. nonspecialist-led) and intensity of follow-up, newer components of survivorship care are being developed that place the patient in the center of treatment planning [9]. This shift in healthcare is generally termed "patient-centered care," which translates into practice as the increased involvement of patients in their own care and treatment, for example, through the use of care plans and patient-reported outcome measures [39].

Below we look at three trends in current survivorship care and look at the emerging evidence for their effectiveness: the implementation of *survivorship care plans and patient education* to potentially improve self-management, the use of *patient-reported outcomes* in follow-up, and, finally, the implementation of *risk-stratified follow-up* to apply resources as effectively as possible by focusing care on those who need it the most.

Survivorship Care Plans and Patient Education

In its seminal 2006 report, *From Cancer Patient to Cancer Survivor: Lost in Transition*, the Institute of Medicine (IOM) recommended that every cancer patient receive an individualized survivorship care plan (SCP) to prepare and help cancer survivors face the challenges of life after cancer treatment [40]. Many types of SCPs have since been developed by different groups but essentially, a SCP typically consists of a summary of the patient's cancer treatment and a follow-up care plan, including information about follow-up visits, symptoms of a possible recurrence, and guidance for maintaining the patient's health [41]. Trials that investigate the use of SCPs also often include some level of patient education, such as a nurse going through the plan with the patient and educating the patients on recommended health behaviors and how to identify worrying symptoms [e.g., 42, 43].

Generally, SCPs have not been shown to be effective in improving patient outcomes and despite the IOM's recommendation, SCPs have not been widely implemented in cancer follow-up [44–46]. None of the available randomized trials investigating the addition of a SCP to cancer follow-up assessed its effect on survival or detection of recurrence, and meta-analyses of SCPs generally reported a lack of effect on a range of outcomes including health-related quality of life, depression, anxiety, self-reported cancer and survivorship knowledge, satisfaction with care, and self-efficacy [9, 45]. However, SCPs may potentially improve survivors' adherence to medical recommendations and have even been shown to improve the health care provider's knowledge of survivorship care and late-effects [45].

The lack of evidence demonstrating positive effects of SCPs has been suggested to be due to incorrect implementation of SCPs and the assessment of the "wrong" outcomes in randomized trials [47, 48]. For example, SCPs were shown to improve "proximal outcomes" such as communication between patient and provider, but not the "distal" outcomes such as self-reported outcomes, e.g., quality of life [47]. A way forward that has been suggested is focusing on the delivery of SCP with an increased focus on survivor engagement and self-management [44]. Indeed, SCPs have been shown to be helpful for patients who cope by seeking information about their disease [49]. Future research may show that implementation of SCPs needs to be more targeted, with an increased focus on patient education, if it is to be an effective component in follow-up care.

Patient-Reported Outcomes in Clinical Care

The use of patient-reported outcomes (PRO) as a clinical tool in patient monitoring and treatment planning is rapidly gaining attention. PROs refer to a physical or psychological outcome that is reported directly by the patient experiencing it, in contrast to an outcome that is reported by a physician or nurse, for example, through a clinical examination [50]. PROs have long been used in oncology research to measure quality of life, physical functioning, and psychological well-being, but the

use of PROs as a clinical tool for optimizing care according to the well-being of the individual patient is relatively new [51]. Since PROs provide a way of capturing the patient's direct experience of his/her symptoms, either through pen-and-paper or electronically, this information can be used to guide treatment such that it is more tailored to the patient's actual condition [52]. PRO information has also been shown to be more accurate than clinician assessment, as several studies have found that clinicians tend to underreport the severity of symptoms compared to the patient [52, 53]. Thus, the use of PROs as a clinical tool may provide a promising way to improve symptom surveillance and management both during and after treatment, potentially leading to better outcomes.

The evidence regarding the effectiveness of PROs in an oncologic setting is still in its infancy. Although three systematic reviews, each based on almost 30 studies, concluded that routine use of PROs improves patient-provider communication, detection of symptoms and patient satisfaction with care, effect sizes for improvements in physical symptoms, psychological symptoms, and quality of life were found to be either small or nonsignificant [50, 54, 55]. However, among patients with advanced cancer, two randomized trials have shown that active symptom monitoring with PROs may improve survival among patients receiving treatment [56, 57]. The results of these studies have yet to be replicated but suggest that PROs can be used to ensure prompt and effective treatment by centering care on the patient's own responses.

Currently, the evidence regarding the active use of PROs in cancer follow-up comes mainly from trials in patients receiving treatment, probably due to the lack of PRO measures that specifically assess survivorship outcomes. However, new trials are underway that are utilizing PRO measures developed for use in cancer survivors and investigating the efficacy of routine PROs in follow-up care [e.g., 58]. As PROs can be delivered electronically and the information can be assessed in real-time, the use of electronic PROs may be a cost-effective way of monitoring cancer survivors and identifying those who need—or do not need—close care [58]. This approach based on stratifying the provision of follow-up care is the topic of the final section of this chapter.

Risk-Stratified Follow-Up Care

The aim of risk-stratified care is to prevent resource waste by identifying and providing close clinical attention to the few patients that need it the most, while supporting the majority of patients in self-management of common survivorship issues [4]. In an environment of sparse healthcare resources, this strategy has been proposed as a way to ensure that follow-up care remains sustainable, while still providing care for the large population of cancer survivors [59]. This personalized approach to care has been adopted in certain countries, although not rigorously investigated. In Denmark, for example, follow-up guidelines for breast cancer survivors were changed in 2016, whereby patients should be offered a follow-up plan based on "needs and personal preference" [60]. Implementation of these broad guidelines

differed around the country, but generally, breast cancer patients with a low risk of recurrence are no longer called in for fixed outpatient appointments (with the exception of scheduled mammograms). Instead, patients are usually provided with healthcare information on how to self-manage common symptoms and a phone number to call in case of worrying symptoms.

The challenge in providing effective risk-stratified care lies in how patients at risk are assessed. Traditionally, personalized medicine has been based on biomarkers or genetic factors. In one of the few randomized trials of risk-stratified follow-up, risk-stratified care in colorectal cancer survivors (i.e., patients considered at high risk of recurrence received intensive surveillance, patients with low risk received low-intensity surveillance) resulted in better overall survival at the same cost compared to patients receiving minimal follow-up regardless of risk of recurrence [61]. However, other than the risk of a cancer recurrence, patients may also be at risk for other negative events, such as late effects and psychological morbidity. Some patients may be vulnerable physically (e.g., patients with severe comorbidity) and psychosocially (e.g., patients with low socioeconomic position and a lack of social support), while others may have low health literacy and are not able to monitor or manage symptoms on their own. These factors need to be remembered when stratifying survivors into long-term follow-up programs. Improving health literacy and involving informal caregivers in cancer follow-up care may be an important component in risk-stratified care [62]. Finally, we need more randomized trials investigating the effectiveness of risk-stratified cancer follow-up and the identification of potentially vulnerable groups.

Conclusion

Routine specialist-led follow-up is becoming unsustainable in light of the increasing number of cancer survivors with complex physical and psychosocial needs. In this chapter, we have seen that new models of care have become complex, with the introduction of new providers and components encompassing both clinical and supportive care. However, the evidence regarding the effectiveness of newer models of care is difficult to synthesize due to the limitations and heterogeneity of the available trials, especially with regard to the different outcomes that are investigated and how they are measured. Trials with adequate power and follow-up are needed to assess outcomes such as survival and detection of recurrence, while the use of standardized PRO measures will help advance the assessment of outcomes such as anxiety, depression, and quality of life.

Future follow-up care is likely to be determined by economic drivers and risk-stratified care may be a solution, whereby resources are distributed based on the complexity of the patient's needs. An assessment of risk or need should not only be based on illness characteristics (e.g., tumor stage or treatments received), but also on whether the patient is socially or psychologically vulnerable. The clinical use of PROs may be an inexpensive way of monitoring identifying vulnerable patients in the follow-up clinic and the active use of care plans and patient symptom education

may help support able patients in self-management and self-reporting of symptoms. However, evidence of the effectiveness of these new models of care is still lacking.

It is also likely that the current evidence on cancer follow-up will change, as ongoing improvements in cancer detection and treatment are expected to improve survival and decrease recurrence rates. Furthermore, new treatments will influence the profile of side and late-effects that we see today, potentially affecting quality of life. As evidence for the effectiveness of different follow-up models on outcomes like survival and recurrence detection take many years to collect, it is important to focus on supporting the physical and psychosocial well-being of cancer survivors in the meantime. New multidisciplinary and stratified ways of delivering follow-up care, such as through the engagement of different providers according to need (e.g., GP, nurse, etc.), as well as monitoring through different platforms (e.g., electronic PRO measure, etc.), may provide the way forward. Finally, it is important to evaluate the implementation of new models of care to strengthen the evidence base.

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Rehabilitation: Definition, Goals, and Timing

9

Georgia Schilling

Introduction

Scientific progress resulted in amazing cancer survival due to advances in systemic treatment, targeted therapy and immunotherapy, complex multidisciplinary therapy approaches in metastatic settings and better screening. The amount of cancer survivors, who are cured or living with cancer as a chronic disease is rising fast: at the beginning of the 70s 5-years overall survival was less than 50% but increased significantly during the last decades. Today we can provide long-term survival to 61% of men and even 66% of female patients. For many of them, cancer diagnosis and its treatment with acute toxicities, side effects, physical and psychosocial sequelae result in sustainable problems or disabilities in activities of daily life (ADL) during and after successful treatment.

Cancer survivors are facing a wide range of individual impairments and must deal with various burdens and needs (shown in the former chapters of this handbook). Rehabilitation plays a main role in maintaining and improving their quality of life and mitigate the loss of function and disability. The group of cancer patients is very demanding and among other chronicle patient groups, the medically most complex to treat:

Oncology-directed treatments introduce a variety of side effects that can adversely impact multiple body systems during and after treatment and each treatment modality (e.g., surgery, radiation, chemotherapy, etc.) may individually or collectively introduce risk for further safety issues. Although a complex array of biosocial factors such as an individual's preexisting comorbidities, polypharmacy, and other lifestyle factors impact and amplify the risk of adverse side effects during treatment and rehabilitation.

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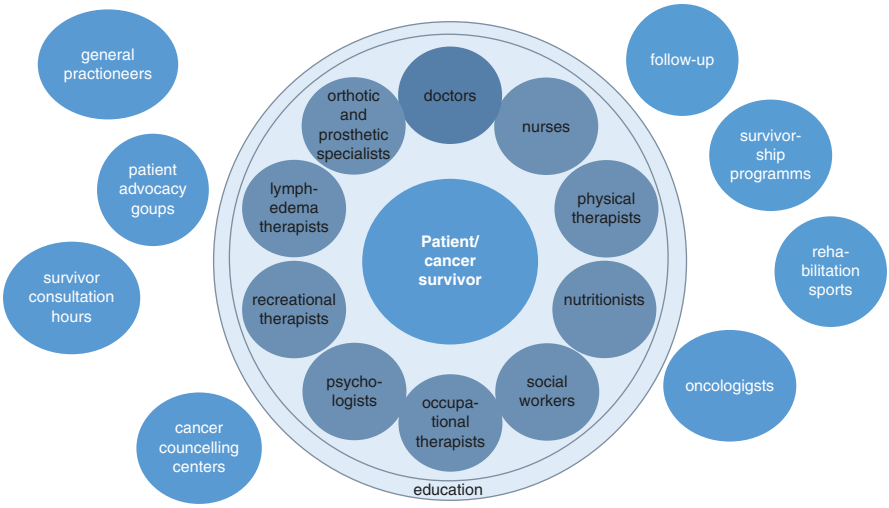

Fig. 9.1 Rehabilitation and additional facilities for after cancer care

During the last 25 years, the perception of rehabilitation in cancer patients fundamentally changed: previously recognized as a spa or wellness therapy after oncological treatment it is now well accepted as the third column of therapy next to in- and outpatient medicine. It defines the beginning of cancer survivorship.

In times of personalized medicine/oncology cancer rehabilitation is an essential component of individualized treatment and follow-up of specific problems after cancer.

Treatment and prevention of disability and its rehabilitation require a comprehensive and multidisciplinary approach, including physical and occupational therapists, speech and language therapists, lymphedema therapists, and further supportive services as nurses, recreational therapists, nutritionists, social workers, mental health professionals, orthotic and prosthetic specialists, vocational counselors, support groups and educational outreach programs. The multiprofessional and interdisciplinary facilities of the cancer survivorship network are shown in Fig. 9.1. Treatments aim to reduce physical disturbances, psychosocial sorrows, and seek to increase possibilities of work reintegration.

Salutogenesis as a Strategy of Rehabilitation

Rehabilitation is based on the principle of salutogenesis. Salutogenesis is the doctrine of convalescence. The term was coined in the 1980s by Aaron Antonovsky (1923–1994), a professor of medical sociology, complementary to "pathogenesis." He focused on the influencing factors comprehensibility, manageability, and meaningfulness as a sense of coherence for the development of health and defined the model of salutogenesis based on these factors [1]:

- *Comprehensibility*: a belief that things happen in an orderly and predictable fashion and a sense that you can understand events in your life and reasonably predict what will happen in the future.
- *Manageability*: a belief that you have the skills or ability, the support, the help, or the resources necessary to take care of things, and that things are manageable and within your control.
- *Meaningfulness*: a belief that things in life are interesting and a source of satisfaction, that things are really worthwhile, and that there is good reason or purpose to care about what happens.

The concept of salutogenesis enriched and supported the medical and rehabilitation science view on health and illness. Salutogenesis is a key element of bio-psychosocial models, focusing on factors that support human health and well-being, rather than on factors that cause disease (pathogenesis). More specifically, the "salutogenic model" is concerned with the relationship between health, stress, and coping.

Definition of Rehabilitation

The WHO has defined rehabilitation as "the use of all means aimed at reducing the impact of disabling and handicapping conditions and at enabling people with disabilities to achieve optimal social integration" [2].

Rehabilitation is based upon the bio-psychosocial concept of the ICF (international classification of functioning disability and health) taking all individual contextual factors into account. The ICF comprehends health conditions, body functions and structures, activity, participation, personal and environmental factors and offers a foundation for the understanding of functioning, disability, and health. It complements the ICD (International Classification of Diseases) and provides a conclusive theoretical, and conceptual framework which incorporates biological, individual, and social aspects of health conditions [3, 4]. In terms of the ICF-model, rehabilitation can be defined as a coordinated process, which enhances activity and participation.

Based on the bio-psychosocial model of the WHO (Fig. 9.2) and a holistic approach, cancer rehabilitation comprises multidisciplinary efforts including, among others, medical, psychological, and physiotherapeutic treatment as well as occupational and functional therapy, depending on the patient's functional status. The aim of cancer rehabilitation is to regain maximal functioning according to the patient's individual resources and needs.

Cancer rehabilitation follows cancer treatment or takes place in between the various treatment modules, e.g., between surgery and adjuvant systemic treatment. The key of the rehabilitation process is to enable patients to include learnings into their daily life practice (at home, at work, in social activities) [5]. This significantly increases the possibilities for patients to integrate into society again.

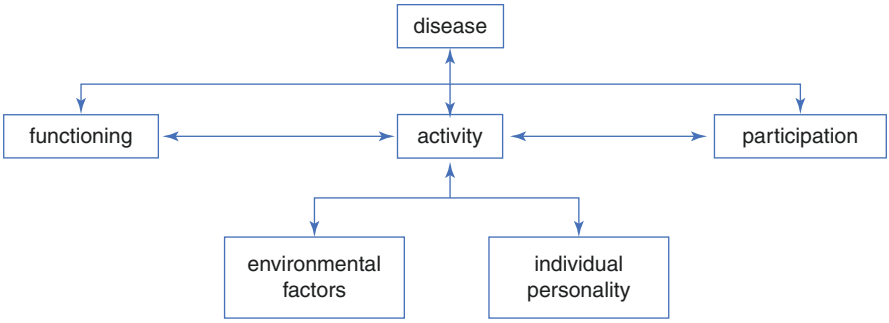

Fig. 9.2 The bio-psychosocial model of the ICF

Cancer rehabilitation has been defined as a distinct field of medicine [5] that focuses on reducing or eliminating (long-term) side effects of cancer itself or its treatment and improving survivor's strength, ability to function, and quality of life. Using an interdisciplinary model of care, professionals identify patients' resources and goals to develop a patient-centered plan of care including medical, physical, psychological, and social components.

Comprehensive cancer rehabilitation is a concept that is defined by the patient. It implies helping a person with cancer to obtain a maximum physical, social, psychological, and vocational functioning within the limits imposed by the disease and its treatment [6]. The ultimate goal is to improve multiple dimensions of life satisfaction.

There are three forms of rehabilitation: Inpatient, outpatient, and self-managed rehabilitation.

At the first time, already in 1978, Lehmann and his coworkers described the need for cancer rehabilitation [7]. More than 50% of patients assessed in cancer referral centers had physical medicine and rehabilitation problems as a general weakness (35%), problems in ADL (30%), deficits in transfers (7%), and 52% had psychological problems. Twenty-five years later this has not changed yet. Cancer patients still show the following disorders: deconditioning in 76%, mobility impairment in 58%, needs for increased ROM in 42%, and deficits in ADL in 22% [8]. Main issues cover common functional impairments like fatigue, pain, polyneuropathy, cognitive impairment, or eating disorders, which can occur in different entities or focus on specific, e.g., dysfunctions after breast cancer surgery, digestive disorders due to gastrointestinal resections or incontinence.

Goals

The main objective of cancer rehabilitation should be the achievement of the highest functional status possible within the limits of the disease and the patient's choices. To make cancer rehabilitation humane and effective it should be dynamic, realistic, and clinically appropriate. The treatment must be developed together with the

Table 9.1 Examples of general and disease-specific goals

General goals concern	Disease-specific goals concern
Fatigue	Urinary incontinence
Mobility	Fecal incontinence
Polyneuropathy, ataxia	Lymphedema
Pain	Speech and swallowing impediments
Gain/lose weight	Feeding problems
Smoking cessation	Arthralgias/musculoskeletal syndrome
Independency	Axillary web syndrome
Self-care activities	Postmastectomy syndrome
Workability	Dropped head syndrome
Participation in social life	Spinal accessory nerve palsy
Return to work	
Social isolation	
Psychosocial stability	
Fear of progression	
Deconditioning	
Cognitive dysfunction	
Balance and coordination deficits	

patient to find the most suitable rehabilitation approaches. Many goals are common to most malignancies, e.g., reducing the functional impact of aerobic deconditioning and chemotherapeutic neuropathy. Others are highly disease-specific such as scapular stabilization following cranial nerve IX sacrifice. Expectations of patients and clinicians must evolve in response to the progression of the disease. Restorative, supportive, preventative, and palliative goals should be reevaluated at critical points along the disease course.

The goals of cancer rehabilitation remain broad and holistic: cancer patients are a heterogeneous group with respect to medical, sociodemographic factors, and rehabilitation needs.

In addition to physical problems that patients may face depending on the type of cancer and treatment, it has been estimated that some 25% of patients are emotionally distressed during and after treatment of cancer [9]. Fatigue is the most prevalent cancer-related symptom and has a significant adverse impact on patients' functional ability [10, 11].

We distinguish between general goals concerning all entities equally and specific goals, due to the different diseases and their impairments in functioning (Tabel 1).

Examples of general and disease-specific goals are shown in Table 9.1.

Timing

Cancer rehabilitation plays an important role throughout the continuum of cancer survivorship. Cancer patients might be in continuous need for rehabilitation during their entire life following the diagnosis of primary cancer, although requirements

for rehabilitation efforts may vary over time. Rehabilitation can be applied in the entire phase of the disease, from the time of diagnosis until the terminal stage. According to the so-called Dietz classification based on patients' physical and individual needs [12], one can distinguish four different categories: preventive, restorative, supportive, and palliative.

Preventive Rehabilitation

Preventive rehabilitation is also referred to as prehabilitation or prospective surveillance. Its emphasis is to prevent or delay complications due to cancer or its therapies. The rationale is that earlier protection of impairments makes them easier to treat, which may prevent future impairments or may reduce their incidence or severity.

Restorative Rehabilitation

Restorative rehabilitation is for patients in whom a full recovery of functioning is expected. Maximum efforts should be exerted to achieve functional recovery.

Supportive Rehabilitation

Supportive rehabilitation focuses on the reestablishment of functional independence in patients with permanent deficits. This means to increase self-ability and mobility. It is used for patients, whose impairments of function and declining abilities have been progressive, due to growing cancer or because of further therapies needed.

Palliative Rehabilitation

Palliative rehabilitation enables patients in an end-of-life setting to maintain a high quality of life as much as possible. This includes symptom control and pain management, physical, social, and psychological issues. The goals are to maximize patient comfort and caregiver support.

Today prehabilitation seems to play a subordinate role in patients with cancer. First, even when a cancer diagnosis is not an emergency, therapy, e.g., surgery of malignant tumors or neoadjuvant treatments should not be delayed for a long time.

Second, the minority of cancer patients can psychologically withstand a postponement of their treatment. Last, we do not have enough data to prioritize prehabilitation over post-acute care, even not in fragile or elderly patients [13].

Post-acute care starts immediately after surgery, radiotherapy, or chemotherapy. The purpose is to prevent impairments or, e.g., enable early postoperative ambulation or improve physical functions [14]. In this phase, many patients become

psychologically depressed because of their cancer diagnosis or changes in their body image and psychological support becomes essential. It is vital to provide patients with information about further consultation possibilities if they suffer from fear of recurrence or long-term sequelae after being discharged [15].

Timings for post-acute treatment should be reviewed for patients with multimodal treatment approaches. Guidelines are open, to start restorative rehabilitation after the whole therapy or immediately after surgery, before adjuvant treatment, which means within the time gap between resection of a malignant tumor and further systemic treatment. Randomized clinical trials, investigating post-acute treatment after surgery vs. after adjuvant treatment are needed to answer open questions urgently.

Rehabilitation during systemic treatment aims to encourage ambulation consistent with the patient's condition to prevent disuse syndrome and maintain physical and muscle strength. An implementation of exercise and sedentary occupational therapy is key to rebuild physical strength, which diminishes during chemotherapy as a result of acute adverse side effects. The aim is to make movement a habit by incorporating physical activities that the patient enjoys in daily life.

Patients with recurrent or advanced cancer experience a variety of symptoms associated with cancer progression but also due to continuous systemic treatment. They suffer constantly from side effects such as myelosuppression, pain, nausea, or polyneuropathy. It is desirable to maintain as much self-care as possible in everyday life. According to shared decision-making, the patients should be encouraged and enabled to accept their resources and barriers and to identify their goals. The rehabilitation approach should acknowledge the surroundings of the patient, the remaining functional activities as well as the available human support like caregivers, caring organizations, or health care devices.

In the terminal stage, the needs of patients and their families should be the main focus of rehabilitation. Even if a patient's condition deteriorates it is possible to perform rehabilitation by palliative care interventions such as range of motion (ROM) exercises for the patients' limbs, massages or breathing assistance [14].

Table 9.2 summarizes the possible contribution of rehabilitation in different disease settings.

Table 9.2 Contribution of rehabilitation in the course of cancer (adopted from [16])

Disease setting	The possible contribution of rehabilitation
Treatment	– Preserving and restoring functioning through exercise and increased physical activity
Post-(acute) treatment	– Developing and supporting a program to help restore daily routines and activities of daily life (ADL) – Fostering return to work – Addressing psychosocial needs – Educating in tertiary prevention – Supervising a maintenance program of exercise and mobility management
Recurrence/advanced disease	– Restoring functioning/preventing its decline
End-of-life	– Maintaining independence and quality of life – Symptom control – Educating caregivers

Forms of Rehabilitation

In the following sections, three different forms of rehabilitation will be reviewed regarding their historical background and results, looking at available clinical studies.

Institutional Cancer Rehabilitation

In Germany rehabilitation is integrated into the comprehensive social security system financed by the statutory pension insurance agencies, driven by their interest to prevent early retirement. Based on this historical background, the German rehabilitation system evolved as a specific and independent system, which is unique and distinct from the system in many other European countries where rehabilitation is a part of primary health care [17, 18]. The rehabilitation usually lasts for 3–4 weeks and includes 2–3 h treatments per day. It occurs in specialized rehabilitation clinics, which are staffed with multidisciplinary rehabilitation teams. The individualized and multidimensional therapy includes a combination of physical training, psycho-oncological interventions, lessons on general health behavior, and coping with cancer. This also applies to Austria or Switzerland. Only 1% of all cancer rehabilitation measures in Germany are carried out in an outpatient setting [19]. The multimodal individualized program for each patient depends on his condition. Functioning needs are assessed at the beginning of the rehabilitation measure and partly at the end of the measure. The decisive advantage of this treatment setting might be the separation of the patient from his normal life. No bothersome influences, no onerous factors jeopardize the rehabilitation process and success. Otherwise, patients are also separated from their families which might be a stressor for some of them.

The results of a number of German evaluation studies indicate that cancer rehabilitation leads to improved physical and psychological quality of life and general well-being in cancer patients [20–23]. But many of the studies suffer from methodological flaws, mainly the lack of control groups and randomized designs.

Studies show so far that besides achieved effects, reached goals are not sustainable. Without any further treatment, the positive mental and physical outcomes drop to the initial level within a short interval [24].

Outpatient Cancer Rehabilitation

Outpatient cancer rehabilitation is suitable for cancer patients who are not in need of care anymore and do not require hospitalization or medical care 24/7. There is a need for interdisciplinary and multidisciplinary support, however. Outpatient cancer care can take place following inpatient rehabilitation for the purpose to shorten it and to make it sustainable. While cancer rehabilitation for example in Germany is offered almost exclusively as an inpatient program (3–4 weeks) for historical

reasons, notably in Scandinavian nations it is provided as an outpatient intervention program: Sweden, Norway, and the Netherlands carry out rehabilitation as primarily outpatient programs. In Finland, Denmark, Iceland, and Norway weekly courses are offered. Cancer rehabilitation takes place at specialized centers and is offered alongside daily living and work over several months or sometimes over 1–2 years [25–27].

In Denmark, the National Board of Health conducted a systematic review focusing on studies that investigated different intervention programs against depression, to increase physical activity or to treat long-term and late effects of cancer therapies. They stressed the need to gain more evidence about types of interventions, their timings, intensity, and duration [25].

Different data from a Danish rehabilitation center offering a short course of 1 week with dietary counseling, physiotherapy, and psychosocial support did not show long-lasting effects with regard to the quality of life or health behavior [9, 10].

A number of studies of multimodal rehabilitation programs published by the Swedish Cancer Society showed mixed results [28–30].

Norwegian research mostly addressed the effects of single interventions and not multidisciplinary programs.

In Finland, various studies investigated the effectiveness of cancer rehabilitation and demonstrated an immediate improvement of quality of life and physical well-being but have not looked into the long-term effects.

The Netherlands' rehabilitation program covering in- and outpatient settings showed positive short- and long-term results on quality of life, physical functioning, and fatigue [31, 32].

Evaluation studies across Europe cover a wide range of interventions and programs, ranging from specific treatments to multidimensional rehabilitation programs covering several interventions from physical exercise to recreation training and psycho-education.

Research in this field suffers from methodological limitations and a lack of data on the effects in both the short- and long-term. Currently, the main challenge in rehabilitation research is to evaluate the diversity of services in terms of contents and effects. Future research is needed urgently and should focus on multimodal programs in different settings in randomized trials [25].

Self-Managed Rehabilitation

The goal of self-management is to empower patients to achieve optimal health and well-being while living with a chronic disease. Self-management involves three fundamental tasks: medical management, role management, and emotional management [33]. Interventions to promote self-management should incorporate education to increase the patient's knowledge of the disease, of available support by health care systems, and training to acquire problem-solving and decision-making skills [34].

Self-management interventions are fundamentally behavior change interventions, designed to help the patient learn and adopt a set of health practices to daily life.

Effective self-management interventions in other chronic disease populations can be transferred into cancer rehabilitation easily. But the evidence for this assumption is still missing. Several recent reviews of self-management interventions in cancer survivors demonstrated mixed results on the effectiveness [35].

An evaluation and systematic review of intervention content and theories by the same group [36] revealed several deficiencies in the clinical trials conducted and published so far. These studies did not include the investigation of behavior change techniques, the participants were predominantly female breast cancer patients and outcomes were missing. Therefore, it is difficult whether to recommend this kind of rehabilitation should be integrated into standard cancer care and to draw definitive conclusions. To increase generalizability, it is needed to assess different tumor entity groups, and the impact of different types of self-management programs on cancer survivors as well as to measure short- and long-term outcomes. The sustainability of the interventions reviewed was poor, suggesting that cancer survivors require interventions that can be applied in their daily activities [37].

In summary, there is a pressing need for more research on different rehabilitation settings to provide more evidence about the most effective type.

The key to success, sustainability, and effectiveness of cancer rehabilitation might be the combination of different settings in- and outpatient intervention with self-management programs in the long-term run of cancer rehabilitation.

A Universal Rehab Plan for Cancer Patients: What Is Evidence-Based for Everyone?

Rehabilitation programs have been proven to be beneficial for a series of other chronic diseases already. In addition, previous reviews on single interventions such as exercise [38] or psychological therapies [39] have shown positive outcomes for patients with cancer.

This drives the assumption that combined physical and psychological interventions in a multimodal rehabilitation program add value and benefits to cancer patients.

The EUROCHIP-3 Working Group on Cancer Rehabilitation has developed specific indicators to evaluate rehabilitation success, including quality of life, return to work, and satisfaction of specific rehabilitation needs (e.g., physical, psycho-oncological, dietary, and speech and language therapy [40]). Hence, to meet the requirements of successful cancer rehabilitation, the programs should consist of multidisciplinary efforts including medical, psychological, and physiotherapeutic treatment as well as occupational therapy, dietetics, and social work [25].

Scott and coworkers [41] conducted a Cochrane Review on multidimensional rehabilitation programs (MDRPs) for adult cancer survivors. They wanted to evaluate the effectiveness and added value of MDRPs in order to facilitate the development of evidence-based cancer rehabilitation. The investigators identified 12 studies examining the effectiveness of MDRPs in terms of maintaining or improving the

physical and psychosocial well-being of cancer survivors to be suitable for the review. These involved participants with a range of cancer diagnoses who received a wide variety of interventions that were delivered using various methods, over different time periods and were assessed using numerous outcome measures. Despite this heterogeneity, the authors were able to pool data on the SF-36 in five of the studies: Participants who received a multidimensional rehabilitation intervention showed a consistent improvement in their physical functioning following the intervention compared to control participants. The reviewed articles suggest that MDRPs are more likely to help patients cope with their physical needs than their emotional needs. MDRPs which looked at one specific behavior area with a unidimensional focus, such as diet, physical activity, or stress, appeared to be more helpful for patients than programs that attempted to address several different behaviors. They seemed to be more successful in terms of generating a positive change in the aspect directly related to their focus or primary aim. Rehabilitation programs that involve participants with a variety of cancer diagnoses show at least similar positive improvements in physical to cancer site-specific programs. The positive effects of rehabilitation programs appear to plateau after approximately 6 months. The type of healthcare professional does not appear to influence the delivery outcome of rehabilitation programs. Successful MDRPs usually involved face-to-face contact between a patient and a health professional (usually a nurse or physical therapist) and included at least one follow-up phone call. Programs which took place over a longer time period (more than half a year), or which delivered by a specific type of health professional, or were delivered to a single cancer site were more successful than brief, focused MDRPs delivered to mixed groups of cancer patients [41].

In contrast, Austrian investigators recently found that MDPR including various aspects of physical and psychological treatment, but also dietary counseling, social work, and occupational therapy, improved scores in all domains as assessed by the EORTC QLQ-C30. The largest differences in that study were found for emotional functioning, social functioning, fatigue, and pain. Moreover, anxiety and depression scores significantly decreased. Type of cancer, age, and sex had no influence on the improvement [21].

In summary, a lot of theoretical studies suggest a substantial positive impact of MDRPs on health-related quality of life in cancer survivors. However, comparative evaluation of different rehabilitation programs did not result in the identification of a single superior type of rehabilitation. Controlled randomized studies are urgently needed to define standards in cancer rehabilitation (which setting in which situation, duration, etc.), to identify the most beneficial interventions, to evaluate the sustainability and long-term effectiveness.

Specific Rehabilitation Goals and Plans for Solid Tumors

According to the bio-psychosocial model of the ICF deficiencies in functioning, activity or social and vocational participation are relevant to determine rehabilitation goals together with the patient in a shared decision-making process.

On admission, a doctor will take a detailed medical history of the current complaint and will ask about other medical problems, that the patient might suffer from. Deficiencies are discussed and analyzed and rehabilitation goals are determined in accordance with the needs and resources of the patient. Depending on the rehabilitation goals, specific therapies and interventions are prescribed. Primary goals are maintaining the ability to work, participation in daily life's activities, or avoiding the need for nursing care.

As mentioned before there are general goals and entity-specific goals.

Therapeutic success is measured by objective investigations like body plethysmography or a 6-min-walk-test, bodyweight, distress assessment, brief fatigue inventory, HADS-score, bodyweight, EORTC QLQ-30, etc., at the beginning and at the end of the rehabilitation process.

Cancer of the Upper Gastrointestinal Tract (GIT)

General goals

- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals

- Learning skills to improve consumption of food and liquids.
- Avoiding malnutrition.
- Understanding the role of Vitamin B12 and why it has to be substituted.
- Understanding the role of digestive enzymes and calcium.
- Information about the normal and the altered digestive function post gastric resection.
- Interpretation of steatorrhea.
- Interpretation of symptoms after upper GIT surgery like cramps as a possible consequence of dumping syndromes, reflux, or incompatible bacteria in the small intestine.
- Improve fine motor skills.
- Reduce polyneuropathy.
- Demonstration and discussion of options for compatibility of work and changed digestive function.
- Preventing osteoporosis.

The following ICF categories are relevant for rehabilitation of upper GIT cancers:

- Dysphagia.
- Impairment of digestive function.

- Malnutrition.
- Symptoms of the digestive tract (meteorism, abdominal cramps, dumping, reflux).
- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognitive function.

Rehabilitation plan comprises
- Health education: nutrition, enzyme substitution, fatigue, polyneuropathy, and upper GIT cancer.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation.
- Nursing care: wound management, bodyweight controls.
- Occupational therapy: perception training, training of balance and coordination.
- Physical therapy: grain mobilization, individual mobilization.
- Nutritional counseling.
- Social service: advice for return to work, medical aids as well as follow-up care, mediation of self-help groups.

Cancer of the Lower Gastrointestinal Tract (GIT)

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Learning skills to improve consumption of non-flatulent foods.
- Avoiding malnutrition.
- Information about the normal and the altered digestive function post large bowel resection (low anterior resection syndrome).
- Information on how to reduce stool frequency and handling stool urgency.
- Improve fine motor skills.
- Reduce polyneuropathy.
- Improve incontinence by pelvic floor training.
- Demonstration and discussion of options for compatibility of work and changed digestive function, increased stool frequency or stool urgency.

The following ICF categories are relevant for rehabilitation of lower GI cancers:

- Impairment of stool consistency, frequency, and continence.
- Impairment of digestive function.

- Symptoms of the digestive tract (meteorism, abdominal cramps, dumping).
- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognition.
- Therapy of erectile dysfunction.

Rehabilitation plan comprises:

- Health education: nutrition, fatigue, polyneuropathy, and lower GIT cancers.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation, sexual advice, and therapy.
- Nursing care: wound management, bodyweight controls, handling the stoma.
- Occupational therapy: perception training, training of balance and coordination, brain-performance training.
- Physical therapy: grain mobilization, individual mobilization, Qi Gong, Thai Chi.
- Nutritional counseling.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Thyroid Cancer

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Reduction of pain and restricted movement in the neck area due to (hemi-) thyroidectomy.
- Treatment of hoarseness and stridor due to injury of the vocal cord.
- Treatment of xerostomia after radiation.
- Avoiding respiratory infection.

The following ICF categories are relevant for rehabilitation of thyroid cancers:

- pain,
- voice functioning,
- functioning of endocrine glands,
- impairment of muscle strength and condition.

Rehabilitation plan comprises

- Health education: fatigue, thyroid cancers.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation, sexual advice, and therapy.
- Nursing care: wound management.
- Occupational therapy: brain-performance training.
- Physical therapy: grain mobilization, individual mobilization, respiratory gymnastics, relaxation of tensions and muscles, lymph drainage, sport and physical activity interventions.
- Speech therapy: voice training.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Lung Cancer

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Smoking cessation.
- Improvement of pulmonary function.
- Reduction of fear of suffocation.
- Learning skills how to deal with dyspnea and panic attacks.
- Pain reduction.
- Improve fine motor skills.
- Reduce polyneuropathy.

The following ICF categories are relevant for rehabilitation of thyroid cancers:

- Pain,
- Dyspnoea,
- Functioning of endocrine glands,
- Impairment of muscle strength and condition,
- Impairment of tentative function and proprioception,
- Impairment of cognition.

Rehabilitation plan comprises

- Health education: smoking cessation, lung cancer, PnP, Fatigue, chronic lung diseases.

- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation.
- Nursing care: wound management.
- Occupational therapy: brain-performance training.
- Physical therapy: grain mobilization, individual mobilization, respiratory gymnastics, relaxation of tensions and muscles, lymph drainage, sport and physical activity interventions.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Prostate Cancer

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Continence training and pelvic floor gymnastics against urinary incontinence.
- Pain management.
- Managing impact of endocrine treatment.
- Managing/therapy of erectile dysfunction.

The following ICF categories are relevant for rehabilitation of prostate cancers:

- Impairment of urinary continence.
- Impairment sexual function.
- Impairment of muscle function.
- Impairment of physical fitness.
- Impairment of micturition.
- pain.

Rehabilitation plan comprises

- Health education: sexual dysfunction, urinary incontinence, endocrine therapy, prostate cancer.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation, sexual advice and therapy.
- Nursing care: wound management.
- Occupational therapy: brain-performance training.
- Physical therapy: pelvic floor training, continence training.

– Nutritional counseling.
– Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Breast Cancer

General goals
– Improving physical abilities.
– Giving information/education with regard to the disease and its treatment.
– Alleviating fatigue.
– Giving coping strategies.
– Reducing psychosocial distress.
– Retrieve ability to work.
– Improving cognitive function.

Specific goals
– Pain management (postmastectomy pain, AI syndrome).
– Reduce polyneuropathy.
– Acquire decongestion stimulating procedures.
– Reduction of lymphedema.
– Support mobility especially in arm and shoulder.

The following ICF categories are relevant for rehabilitation of breast cancer:

– Impairment of lymphatic circulation.
– Impairment of perception.
– Sexual impairments.
– Impairment of muscle function.
– Impairment of tentative function and proprioception.
– Impairment of cognition.

Rehabilitation plan comprises:

– Health education: fatigue, polyneuropathy, and breast cancers, importance of sports and nutrition.
– Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation.
– Nursing care: wound management, bodyweight controls, skincare.
– Occupational therapy: perception training, training of balance and coordination, brain-performance training.
– Physical therapy: lymph drainage, decongestion gymnastics, individual mobilization, Qi Gong, Thai Chi.
– Nutritional counseling.
– Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Gynecological Cancers

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Pain management.
- Reduce polyneuropathy.
- Acquire decongestion stimulating procedures.
- Reduction of lymphedema.
- Continence training and pelvic floor gymnastics against urinary incontinence.

The following ICF categories are relevant for rehabilitation of gynecological cancers:

- Impairment of lymphatic circulation.
- Sexual impairments (dyspareunia, vaginal dryness, etc.)
- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognition.
- Impairment of lymphatic circulation.

Rehabilitation plan comprises:

- Health education: fatigue, polyneuropathy, gynecological cancers.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation, sexual therapy.
- Nursing care: wound management, bodyweight controls, skincare.
- Occupational therapy: perception training, training of balance and coordination, brain-performance training.
- Physical therapy: lymph drainage, decongestion gymnastics, individual mobilization.
- Nutritional counseling.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

GU Cancer

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.

– Alleviating fatigue.
– Giving coping strategies.
– Reducing psychosocial distress.
– Retrieve ability to work.
– Improving cognitive function.

Specific goals
– Pain management.
– Continence training and pelvic floor gymnastics against urinary incontinence.
– Learning skills in handling a nephrostomy or a neo-bladder.
– Learning skills in self catheterization.
– Alleviation of long-term side effects of systemic treatment, surgery, or radiation therapy.

The following ICF categories are relevant for rehabilitation of GU cancers:

– Impairment of micturition.
– Sexual impairments.
– Impairment of muscle function.
– Impairment of tentative function and proprioception.
– Impairment of cognition.
– Incontinence.

Rehabilitation plan comprises:

– Health education: fatigue, GU cancers.
– Psycho-oncological interventions: individual interviews, relaxation techniques, smoking cessation, sexual therapy.
– Nursing care: wound management, bodyweight controls, skincare.
– Occupational therapy: perception training, training of balance and coordination, brain-performance training.
– Physical therapy: stoma therapy, individual mobilization, pelvic floor training.
– Nutritional counseling.
– Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Glioma

General goals
– Improving physical abilities.
– Giving information/education with regard to the disease and its treatment.
– Alleviating fatigue.
– Giving coping strategies.
– Reducing psychosocial distress.
– Retrieve ability to work.
– Improving cognitive function.

Specific goals
- Avoiding deterioration.
- Maintaining autonomy.

The following ICF categories are relevant for rehabilitation of glioma:

- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognition.

Rehabilitation plan comprises:

- Health education: fatigue, glioma.
- Psycho-oncological interventions: individual interviews, relaxation techniques, neuro-psychological training.
- Nursing care: wound management, skincare.
- Occupational therapy: perception training, training of balance and coordination, brain-performance training.
- Physical therapy: individual mobilization.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Head and Neck Cancer

General goals
- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals
- Avoiding deterioration.
- Maintaining autonomy.
- Acquire skills in handling tracheostomy.
- Voice raining.
- Avoiding malnutrition.
- Promoting lifestyle changes.

The following ICF categories are relevant for rehabilitation of head and neck cancer:

- Impairment of voice.
- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognition.

Rehabilitation plan comprises:

- Health education: fatigue, head and neck cancers.
- Psycho-oncological interventions: individual interviews, relaxation techniques, smoking and drinking cessation.
- Nursing care: wound management, skincare, handling the tracheostoma or PEG.
- Occupational therapy: perception training, training of balance and coordination, brain-performance training.
- Physical therapy: individual mobilization.
- Nutritional counseling.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.

Pancreatic Cancer

General goals

- Improving physical abilities.
- Giving information/education with regard to the disease and its treatment.
- Alleviating fatigue.
- Giving coping strategies.
- Reducing psychosocial distress.
- Retrieve ability to work.
- Improving cognitive function.

Specific goals

- Avoiding deterioration.
- Maintaining autonomy.

The following ICF categories are relevant for rehabilitation of pancreatic cancer:

- Impairment of muscle function.
- Impairment of tentative function and proprioception.
- Impairment of cognition.
- Impairment of digestive function.
- Malnutrition.
- Symptoms of the digestive tract (meteorism, abdominal cramps, reflux fatty stools).

Rehabilitation plan comprises:

- Health education: fatigue, pancreatic cancer, fatty stools, diabetes mellitus IIIc.
- Psycho-oncological interventions: individual interviews, relaxation techniques.
- Nursing care: wound management.
- Occupational therapy: perception training, training of balance and coordination, brain-performance training.
- Physical therapy: individual mobilization.
- Social service: advice for return to work, medical aids and follow-up care, mediation of self-help groups.
- Nutritional counseling including the use of pancreatic enzymes and handling pakreakreoprive diabetes.

Figure 9.3 shows an exemplary treatment plan for a woman with papillary thyroid cancer and adipositas. Her impairments in functioning after thyroidectomy and radio-jod-therapy are fatigue, hoarseness, cognitive impairments, and a shoulder-arm-syndrome.

therapy plan — **rehabilitation clinic**

diagnosis **thyroid cancer, adipositas BMI 31, fatigue, hoarseness, shoulder-arm-syndrome, cognitive impairme**

patient: name, surename 12345678

beginning Thursday 08012019
end Monday 8062019

rehabilitation: 01.08.2019 - 22.08.2019

Zeit	Monday, 07.08.2020	Tuesday, 01.08.2019	Wednesday, 02.08.2019	Thursday, 03.08.2019	Friday, 04.08.2019	Saturday, 05.08.2019
08:00			08:30 **house keeping**	08:00 **initial consultation** occupational therapist	08:00 **meditation** phschologist	08:30 **ergometer** physiotherapist
09:00				09:00 **information** social service	09:30 **physical therapy** physiotherapist	09:00 **MTT** physiotherapist
10:00			10:00 **admission interview** physician	10:30 **ergometer** physiotherapist	10:15 **wellcome meeting** management	
11:00			11:30 **MTT - introduction** physiotherapist	11:30 **attending consultation** attending physician 15 min.	11:30 **voice therapy** speech therapist	11:30 **physical therapy** physiotherapist
12:00						
13:00		arrival	13:30 **P distress** psychologist	13:30 **Qi Gong** physiotherapist	13:00 **education nutrition** nutritionist	
14:00				14:30 **pscho-onco module** phschologist	14:30 **outdoor sport** physiotherapist	
15:00			15:00 **aquajogging** physiotherapist	15:40 **hydrojet** masseur	15:45 **lymph drainage** masseur	
16:00			16:30 **P introduction rehab** physician	16:30 **P physical therapy** physiotherapist	16:30 **brain-performance training** occupational therapist	
17:00						

breakfast - 07:00 bis 07:45 h; lunch - 12:00 bis 12:45 h; dinner 17:30 - 18:15 h

therapy plan — **rehabilitation clinic**

diagnosis **thyroid cancer, adipositas BMI 31, fatigue, hoarseness, shoulder-arm-syndrome, cognitive impairme**

patient: name, surename 12345678

beginning Thursday 08012019
end Monday 08222019

rehabilitation: 07.08.2019 - 13.08.2019

time	Monday, 07.08.2020	Tuesday, 08.08.2019	Wednesday, 09.08.2019	Thursday, 10.08.2019	Friday, 11.08.2019	Saturday, 12.08.2019
	08:30 **voice therapy** speech therapist	08:00 **brain-performance training** occupational therapist	08:30 **Qi Gong** physiotherapist	08:30 **E lymph edema** physiotherapist	08:00 **meditation** psycologist	
	09:30 **aquajogging** physiotherapist	09:00 **doctor's visit** physician				09:00 **Qi Gong** physiotherapist
		12:00 **body weight module 2** nutritionist	10:00 **E thyroid cancer** physician	10:00 **outdoor sports** physiotherapist	10:00 **voice therapy** speech therapist	
	11:00 **body weight module 1** phschologist	11:30 **ergometer** physiotherapist		11:30 **brain-performance training** occupational therapist	11:30 **physical therapy** physiotherapist	11:00 **ergometer** physiotherapist
			12:00 **body weight module 3** nutritionist			
	13:20 **hydrojet** masseur	13:30 **meditation** psychologist		13:30 **lymph drainage** masseur	13:30 **body weight module 4** nutritionist	
	14:30 **pscho-onco module 2** phschologist	14:30 **lymph drainage** masseur	14:30 **aquajogging** physiotherapist	14:30 **psycho-onco module 3** psychologist		
		15:00 **physical therapy** physiotherapist			15:00 **aquajogging** physiotherapist	
	16:00 **MTT** physiotherapist	16:00 **outdoor sports** physiotherapist	16:00 **Hydrojet** Masseur (K642D01)	16:00 **MTT** physiotherapist		

breakfast - 07:00 bis 07:45 h; lunch - 12:00 bis 12:45 h; dinner 17:30 - 18:15 h

Fig. 9.3 examplary rehabilitation plan with a 21-days intervention schedule in an inpatient setting

therapy plan

diagnosis **thyroid cancer, adipositas BMI 31, fatigue, hoarseness, shoulder-arm-syndrome, cognitive impairme**

patient: name, surename 12345678

beginning Thursday 08012019
end 8062019

rehabilitation: 14.08.2019 - 20.08.2019

rehabilitation clinic

time			Wednesday, 16.08.2019	Thursday, 17.08.2019	Friday, 18.08.2019	Saturday, 19.08.2019
08:00	10:00 **voice therapy** speech therapist	08:00 **outdoor sports** physiotherapist	08:30 **Qi Gong** physiotherapist	08:00 **outdoor sports** physiotherapist	08:30 **phyical therapy** physiotherapist	
09:00	09:30 **outdoor sports** physiotherapist	09:30 **doctor's visit** physician		09:30 **social counselling** social service	09:00 **lymph drainage** masseur	09:00 **Qi Gong** physiotherapist
10:00			10:00 **E fatigue** physician		10:00 **voice therapy** speech therapist	
11:00	11:00 **body weight module 4** psychologist	11:00 **brain-performance training** occupational therapist	11:30 **ergometer** physiotherapist	11:00 **brain-performance training** occupational therapist	11:30 **ergometer** physiotherapist	11:00 **brain-performance training** occupational therapist
12:00						
13:00	13:20 **hydrojet** masseur	13:30 **meditation** psychologist	13:30 **physical therapy** physiotherapist	13:20 **hydrojet** masseur	13:30 **meditation** psychologist	
14:00	14:30 **psyco-onco module 4** psychologist	14:00 **lymph drainage** masseur		14:30 **pscho-onco module 5** phschologist		
15:00		15:00 **MTT** physiotherapist			15:00 **aquajogging** physiotherapist	
16:00	16:30 **aquajogging** physiotherapist		16:00 **body weight module 5** physiotherapist	16:00 **MTT** physiotherapist		
17:00						

breakfast - 07:00 bis 07:45 h; lunch - 12:00 bis 12:45 h; dinner 17:30 - 18:15 h

therapy plan

diagnosis **thyroid cancer, adipositas BMI 31, fatigue, hoarseness, shoulder-arm-syndrome, cognitive impairme**

patient: name, surename 12345678

beginning Thursday 08012019
end Monday 08222019

rehabilitation: 21.08.2019 - 22.08.2019

rehabilitation clinic

time	Monday, 21.08.2020	Tuesday, 22.08.2019				
08:00	08:00 **meditation** phschologist	departure				
09:00	09:00 **voice therapy** speech therapist					
10:00	10:00 **lymph drainage** masseur					
11:00	11:00 **hydrojet** masseur					
12:00						
13:00	13:00 **discharge visit** physician					
14:00	14:30 **pscho-onco module 6** phschologist					
15:00						
16:00	16:00 **Qi Gong** physiotherapist					
17:00						

breakfast - 07:00 bis 07:45 h; lunch - 12:00 bis 12:45 h; dinner 17:30 - 18:15 h

Fig. 9.3 (continued)

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Symptoms and Symptom Management in Survivorship Patients

10

Gilles Klein and Daniel Jodocy

Fatigue

Here is just a brief summary of cancer-related fatigue. The topic will be discussed in detail elsewhere in this manuscript.

The NCCN guideline for cancer-related fatigue defines fatigue as a distressing, persistent, subjective sense of overwhelming physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning.

A majority of patients will experience some level of fatigue during their course of treatment; however, approximately 30% of patients will endure persistent fatigue for a number of months to years after treatment, which can be extremely frustrating for the survivor and their environment.

All health care providers should routinely screen for the presence of fatigue from the point of diagnosis throughout the therapy and after the completion of therapy. Diagnostic work-up should be done carefully and includes history of fatigue, careful physical examination, assessment of status/risk of recurrence of the initial cancer subtype and exclude treatable contributing factors such as comorbidities, medications (e.g., pain medication, sleep medication, or antiemetics), and substance abuse/alcohol. Consider performing laboratory evaluation based on presence of other symptoms, onset, and severity of fatigue (e.g., complete blood cell count, comprehensive metabolic panel: electrolytes; hepatic and renal function, endocrinologic evaluation: TSH [thyroid-stimulating hormone]).

Treatment consists of specific education about fatigue after treatment. Addressing all medical and treatable contributing factors first (e.g., pain, depression, anxiety, emotional distress, sleep disturbance, nutritional deficit, activity level, anemia, medication

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adverse effects, and organ-related comorbidities). Initiating/maintaining adequate levels of physical activity can reduce cancer-related fatigue in posttreatment survivors. Active encouragement of all patients to engage in a moderate level of physical activity after cancer treatment (e.g., 150 min of moderate aerobic exercises such as fast walking, cycling, or swimming) per week with an additional 2–3 strength training (e.g., weight lifting) sessions per week. Cognitive-behavioral therapy/behavioral therapy and psychoeducational therapies can reduce cancer-related fatigue in posttreatment survivors. Some evidence exists that mindfulness-based approaches, yoga, or acupuncture can reduce fatigue symptoms. There is some data on biofield therapies (touch therapy), massage, music therapy, relaxation, reiki, and qigong improving fatigue. Evidence suggests that psychostimulants (e.g., methylphenidate) and other wakefulness agents (e.g., modafinil) can be used to manage fatigue in patients with advanced disease/active treatment. However, there is very limited evidence of the effectiveness in reducing fatigue in patients after curative treatment. No consistent evidence exists on the impact of supplements such as ginseng, vitamin D, and others [1].

Sleep Disorders

Sleep disturbances occur in about 10–15% of the general population and are often associated with situational stress, illness, aging, and drug treatment [2]. Sleep is vital to all human functioning and encompasses a complex set of physiological and behavioral processes; disruption in one or more of these processes can lead to many different types of symptoms of poor sleep that can occur singly or in combination. In cancer patients, disturbed sleep is rated the second most bothersome symptom based on cancer and treatment status. Consequences of acute and chronic untreated sleep-wake disturbances in individuals with and without cancer include daytime fatigue, irritable mood, and cognitive impairment. When these conditions persist, they may have a negative impact on a person's social life, daily function at work and at home, and quality of life. In the general population, persistent insomnia has been associated with work absences, life-threatening motor vehicle and work-site accidents, and psychiatric and cardiovascular disorders. Importantly, the economic burden of untreated insomnia is much higher than the costs associated with treating insomnia [3]. Since cancer survivors often depend on employment for economic survival and insurance benefits, access to effective treatments for sleep-wake disturbances, insomnia, and sleep disorders is an important factor [4].

Poor sleep is a known problem in cancer patients along the treatment trajectory from the point of diagnosis to the end of life. It is estimated that 30–60% of adults with cancer experience sleep-wake disturbances during diagnosis, treatment, and survivorship. Poor sleep in cancer patients and survivors could be attributed to the presence of one or more underlying sleep disorders [5]. Sleep disorders can be classified using two main classification systems, the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [6] or the International Classification of Sleep Disorders (ICSD) [3], and they can directly impact health-related quality of life. Five major categories of sleep disorders have been defined by the Sleep Disorders

Classification Committee of the American Academy of Sleep Medicine: (1) Disorders of initiating and maintaining sleep (insomnias). (2) Sleep-related breathing disorders (sleep apnea). (3) Disorders of excessive somnolence (hypersomnias). (4) Disorders of the sleep-wake cycle (circadian rhythm sleep disorders). (5) Dysfunctions associated with sleep, sleep stages, or partial arousals [3]. Diagnosing specific sleep disorders usually requires a detailed and specialized evaluation, sometimes requiring overnight evaluation of objective measures of sleep. However, it has been reported that cancer patients often do not get referrals to sleep specialists when presenting with chronic sleep complaints [7]. Insomnia is defined as a persistent difficulty with sleep initiation, maintenance, duration, or quality accompanied by some form of daytime impairment, which occurs despite adequate opportunity for sleep. Insomnia is considered chronic if the problems persist for three or more nights per week for at least 3 months; acute if they have been occurring for less than 3 months [3]. The term sleep-wake disturbances is broader, encompassing perceived or actual alterations in nighttime sleep (quality and duration), with subsequent daytime impairment, without a diagnosis by a specialist. Although sleep-wake disturbances often present with the usual features of insomnia, such as difficulty falling asleep (sleep initiation/latency), difficulty staying asleep (sleep maintenance), not feeling restored or refreshed on awakening, and daytime dysfunction, they also include circadian changes, sleep fragmentation, and other sleep alterations. In clinical practice, distinguishing between sleep-wake disturbances and insomnia is less important than identifying the actual sleep disorder and treating it appropriately [8].

Physical illness, pain, hospitalization, drugs, and other treatments for cancer and the psychological impact of a malignant disease may dysregulate sleeping patterns of patients with malignancy. In contrast, poor sleep adversely affects global mood and physical/mental performances. In the healthy population, persistent insomnia has been associated with a higher risk of developing anxiety and/or depression [9, 10].

Basically, physiologic sleep consists of two phases: (1) Rapid eye movement (REM) sleep: REM sleep, also known as dream sleep, is the active or paradoxic phase of sleep in which the brain is active. (2) Non-REM (NREM) sleep: NREM sleep is the quiet or restful phase of sleep. NREM, also referred to as slow-wave sleep, is divided into four stages of progressively deepening sleep based on electroencephalogram findings.

The stages of sleep occur in a repeated pattern or cycles of NREM phases followed by REM phases, with each cycle lasting approximately 90 min. The sleep cycle is repeated 4–6 times during a 7–8-h sleep period. This sleep-wake cycle is controlled by an inherent biological clock or circadian rhythm. Disruptions in individual sleep patterns can disrupt the circadian rhythm and impair the sleep cycle [11].

Cancer patients are known to be at great risk of developing insomnia and other disorders of the sleep-wake cycle. Insomnia is the most common sleep disturbance in this population and is mostly secondary to physical and psychological factors related to cancer and cancer treatment. Anxiety and depression are often related to insomnia. The etiology and risk factors for sleep-wake disturbances comorbid with cancer are numerous, and these conditions often exacerbate prior sleep issues. Sleep disturbances may be exacerbated by paraneoplastic syndromes and by symptoms associated with tumor invasion

[3, 9, 10]. It is not clear if specific types of cancer are associated with a higher risk for sleep-wake disturbances. Some studies showed that the prevalence of sleep-wake disturbances is more frequent in breast cancer, compared to other cancer types [12]. Obstructive sleep apnea (OSA) has been associated with head and neck cancer [13]. Prostate cancer survivors treated with radiotherapy may experience sleep-wake disturbances resulting from urinary frequency and urgency [14]. Side effects of treatment that may affect the sleep-wake cycle include pain, anxiety, night sweats or hot flashes, gastrointestinal (e.g., constipation, diarrhea, nausea, stool incontinence), genitourinary (e.g., urine incontinence, dysuria, pollakisuria), and chronic respiratory dysfunction or fatigue [15–17]. Medications (e.g., chemotherapy, radiotherapy, antihormonal treatment, corticosteroids, vitamin supplementation, neuroleptics, antiemetics, etc.) [7] or sustained use of sedatives and hypnotics (e.g., benzodiazepines, pentobarbital, Z-substances, etc.) or alcohol abuse may cause insomnia. Withdrawal from some substances may cause insomnia such as antidepressants, opioids, benzodiazepines, and corticosteroids [3]. Hypnotics may interfere with rapid eye movement (REM) sleep, resulting in increased irritability, apathy, and diminished mental alertness. Abrupt withdrawal of hypnotics and sedatives may lead to symptoms of nervousness, seizures, or REM rebound which is defined as an increase of REM sleep phases resulting in higher frequency and intensity of dream phases, including nightmares. During hospitalizations, sleep might be interrupted by treatment schedules, hospital routines, and roommates.

Consequences of sleep disturbances can influence outcomes of therapeutic and supportive care measures. A patient with sleep disturbances may experience irritability and inability to concentrate, which may in turn affect the patient's compliance with treatment protocols, medication, decision-making, and relationships with others [7].

It is important that clinicians and health care providers adopt routine screening and interventions to reduce chronic insomnia and improve the quality of life in cancer survivors. Although sleep disturbances are very common in cancer patients, they continue to be underdiagnosed and undertreated [18–20]. Sleep-wake disturbances are recognized through patients' subjective complaints of insufficient quality or duration of sleep.

Diagnostic work-up: The first step in diagnosing sleep-wake disturbances in patients with cancer is using standardized screening questions such as "Are you having problems falling asleep or staying asleep?" "Are you experiencing excessive daily sleepiness?" "Have you ever been told to be frequently snoring or stop breathing during sleep?"; these questions should be asked at regular intervals and when changes occur in the patient's clinical status. The next step is to detect sleep disorders (e.g., OSA, restless legs syndrome, hypersomnia) and using self-report instruments (such as the Insomnia Severity Index) to determine the severity of sleep-wake disturbances. The most important is the identification of potentially treatable risk factors such as comorbidities, medications, symptoms possibly responsible for the stated sleep disorder. Controlling comorbidities or reducing doses of medications that might have stimulating or sedating side effects (e.g., corticosteroids, opioids, antidepressants, antiemetics, antihistamines) may improve sleep patterns. Health care providers should monitor and treat reversible symptoms such as pain, fatigue, and depression [4].

Treatment of sleep-wake disturbances that are comorbid with cancer has advanced steadily in the last two decades. Sleep hygiene and education is most fundamental for all patients [21–23]. Cancer patients suffering from sleep-wake disturbances may benefit from treatments originally developed for adults without cancer. Non-pharmacological [4, 24, 25] and pharmacological interventions [26] can improve poor sleep occurring simultaneously with cancer. Cognitive-behavioral interventions (CBI) consist of a multicomponent therapy aimed at changing negative sleep-related thoughts and behaviors. It can lead to sustained improvements in sleep duration and sleep quality [27]. Components of CBI include sleep restriction, stimulus control, sleep hygiene education, and cognitive therapy, with or without relaxation [27, 28]. These components reduce the hyperarousal and other factors that perpetuate sleep-wake disturbances by modifying sleep schedules, habits, and dysfunctional misconceptions. Combining CBI with medications can further improve outcomes, but there is only scarce evidence to this approach [27]. Furthermore regular exercise and mindfulness-based stress reduction (MBSR) are useful tools [22]. Aerobic exercise improves mental and emotional health in stressful times and can strengthen daily circadian activity rhythms [29]. MBSR is a flexible and customizable approach to stress reduction. It is composed of two main components: mindfulness meditation and yoga and might improve cancer-related sleep-wake disturbances, particularly helpful in patients with anxiety, although evidence is scarce [22]. Sedatives and hypnotics may be beneficial as short-term interventions to treat sleep-wake disturbances and are mostly used in conjunction with sleep hygiene and other non-pharmacologic strategies that take longer to show benefits (Table 10.1). Short-acting agents should be preferred for sleep initiation and long-acting agents for sleep maintenance.

Table 10.1 Pharmacological treatment of cancer-related sleep disturbances [4]

Drug	Dosing	Main characteristics	Side effects
Nonbenzodiazepine receptor agonists			
Zolpidem tartrate	5–10 mg PO	Short-acting, sleep Initiation only	Headache, dizziness, CNS depression, and cognitive/motor impairment CYP3A4 substrate (interactions!)
Zaleplon	5–20 mg PO	Short-acting, sleep initiation only	Headache, dizziness, nausea, abdominal pain
CNS depression and cognitive/motor impairment			
Zopiclone	3.75–7.5 mg PO	Long-acting, sleep initiation and maintenance	Metallic taste, headache, dizziness, hang-over, CNS depression, and cognitive/motor impairment CYP3A4 substrate (interactions!)
Benzodiazepine			
Temazepam	7.5–30 mg PO	Prolongs total sleep time, anxiolytic, muscle relaxant	CNS depression; cognitive/motor impairment Tolerance, dependence, and withdrawal
Tricyclic antidepressant			
Doxepin	3–6 mg PO	Sleep maintenance, Antidepressant effects	Anticholinergic effects (e.g., constipation and urinary retention), weight gain, CNS depression
Melatonin agonist			
Melatonin	3–5 mg PO	Sleep initiation only, barely affects cognitive/motor function	Somnolence, dizziness, nausea, fatigue, and headache CYP1A2 substrate (interactions!)

Anxiety/depression should be treated with adequate medications [4]. The preferred classes of drugs for short-term use (7–14 days) should be benzodiazepines and non-benzodiazepine receptor agonists ("z-substances"). Potential serious adverse effects of sedative/hypnotic medications should be discussed with patients including sleep-related behaviors (e.g., sleep-driving, worsening of depression, or psychological/physical dependence). Medications should be started at low doses, monitor patients closely for side effects, and tapering slowly to prevent withdrawal symptoms and rebound insomnia. Hypnotics and sedatives can lead to a hangover effect which may result in reduced memory, physical/psychological performance, leading to impaired daytime functioning. Herbal medications should not be prescribed because of a higher risk for drug–drug interactions [20, 21].

Depression and Anxiety

Mental health issues such as cancer-related distress along with anxiety and depression are very prominent among cancer survivors. With the rising numbers of cancer survivors due to the improvement in curative cancer treatments, increasing prevalence of anxiety and depression in this population will result. Health care providers need to address these problems, because of their potential consequences on qualitiy of life, return to normal daily activities, adherence to treatment/follow-up visits, and a higher risk of suicide among cancer survivors [30].

During cancer treatment patients experience intensive support from health care providers (e.g., oncology nurse, physiotherapist, oncologist) and family environment. Their focus and daily routines are mostly packed with medical visits, treatment schedules, dealing with treatment side effects, and expectation in a curative ending of the disease. After curative treatment, many cancer survivors experience loneliness or feel abandoned because cancer-related distress is suddenly lacking. Fear of recurrence (FOR) and hypervigilant status on physical sensations can aggravate these feelings [31].

The National Comprehensive Cancer Network (NCCN) distress guideline describes distress as a continuum, ranging from common feelings of vulnerability, sadness and fears of recurrence to disabling depression, anxiety, trauma, panic, and existential crisis [32].

According to the DSM-V catalog depression is defined as:

- Feeling sad or having a depressed mood
- Loss of interest or pleasure in activities once enjoyed
- Changes in appetite—weight loss or gain unrelated to dieting
- Trouble sleeping or sleeping too much
- Loss of energy or increased fatigue
- Increase in purposeless physical activity (e.g., inability to sit still, pacing, hand-wringing) or slowed movements or speech (these actions must be severe enough to be observable by others)
- Feeling worthless or guilty

- Difficulty thinking, concentrating, or making decisions
- Thoughts of death or suicide

Symptoms must last at least 2 weeks and must represent a change in the previous level of functioning for a diagnosis of depression. A major depression is diagnosed with at least five symptoms present [33].

According to the DSM-V catalog generalized anxiety disorder is defined as:

Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months. The individual finds it difficult to control the worry. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

- Restlessness, feeling keyed up or on edge
- Being easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep) [33]

Risk factors for cancer-related depression and anxiety according to the Pan Canadian Practice Guideline Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) In Adults with Cancer are:

- Living/Family condition: living alone, dependent, financial problems (poor socioeconomic status), change in family status
- Marital status: single, separated, divorced, or widowed
- Withdrawal statutes: alcohol, substance use
- Vulnerable points: disease recurrence, advanced or progressive disease (metastases), moving toward palliative or hospice care, cumulative stressful life events, change in functioning or roles
- Past Medical and Psychological History: panic attacks, Generalized Anxiety Disorder (GAD), history of depression, history of mood disorder, history of other psychiatric disorder
- Medical conditions: comorbidity (severe illnesses), prolonged treatment phase, cognitive impairment, surgical interventions, treatment side effects, current medication associated with anxiety or depression, or seeing a specialist
- Other factors: younger age, female, lack of social support, poor marital or family functioning, poor communication with the health care team, lack of supportive network, poor control of pain or other symptoms, family/caregiver conflicts, communication barriers, catastrophizing coping or anxious coping style (language, literacy, physical) [34]

Diagnostic work-up: A firm clinical interview should be the first step in screening for anxiety and depression. Numerous standardized questionnaires for screening and diagnosing mental health problems exist for the general population. In cancer patients some of them have been validated. The National Comprehensive Cancer Network (NCCN) recommends the distress thermometer (DT) to measure cancer-related distress [35]. It is a numerical rating scale (NRS) ranging from 0 (no distress) to 10 (extreme distress) with a cutoff of five points. It should be used as a brief and fast screening tool, although it has a low sensitivity and specificity in cancer patients [36]. Alternatively the Patient Health Questionnaire (PHQ)-4 consists of two key depression and anxiety symptoms required according to the DSM-V. For the PHQ-4, a cutoff of three or more shows good sensitivity and specificity. Both tests, DT and PHQ-4 should be used for fast screening, but do not constitute sufficient tools in diagnosing anxiety and depression [37].

More complex questionnaires such as the PHQ-9 [38] or Hospital Anxiety and Depression Scale (HADS) [39] have been studied in cancer survivors. The PHQ-9 for instance was studied in hematopoietic cell transplant survivors and showed promising results. Screening for anxiety and depression can stimulate discussions between survivors and health care providers about experienced concerns [38].

Differential diagnosis can be difficult in cancer survivors because some of the symptoms of anxiety and depression overlap with other problems reported (e.g., cognitive difficulties, cancer-related fatigue, sleep disturbances, treatment side effects, substance abuse, etc.). Other medical conditions (e.g., hyperthyroidism, VitB12 deficiency, chronic infections, anemia, etc.) should be ruled out [31].

Treatment of anxiety and depression in cancer survivors are based on non-pharmacological and pharmacological options. Most studies have been conducted in women with breast cancer patients [31].

Non-pharmacological treatment (Table 10.2): Physical activity may reduce depressive and anxiety symptoms in breast cancer survivors [40], although a study in cancer survivors with prostate cancer had no effect on mood improvement by physical activity intervention [41]. Mindfulness-based approaches have shown efficacy in reducing anxiety and depressive symptoms in breast cancer and colorectal

Table 10.2 Non-pharmacological and pharmacological interventions for depression and anxiety in cancer survivors [31]

Type of intervention	Cancer populations with evidence	Indication
Cognitive-behavioral therapy	Breast cancer, hematopoietic cell transplant	Depressive symptoms, anxiety, post-traumatic stress
Mindfulness-based stress reduction	Breast cancer	Depressive symptoms, anxiety
Hypnosis	Breast cancer	Depressive symptoms
Self-management	Breast cancer, mixed cancer sites	Distress
Physical activity	Breast cancer	Depressive symptoms, anxiety
Gabapentin	Breast cancer	Anxiety

[42–45]. Cognitive-behavioral therapy is also an effective option in reducing depression symptoms in cancer survivors [46, 47]. Hypnosis has shown to reduce anxiety symptoms in a cohort of breast cancer survivors [48]. Nowadays web-based interventions and education may be attractive for psychosocial interventions because patients already use Internet resources for cancer information [49].

Pharmacological treatment: medications used in depressive and anxious non-cancer patients have also shown efficacy in cancer survivors. Selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) used for reducing hot flashes in breast cancer survivors on antihormonal therapy can reduce depressive symptoms [50]. No increased recurrence rates in women taking tamoxifen in combination with antidepressants which are metabolized by cytochrome P450 enzymes (fluoxetine, sertraline, bupropion, paroxetine) are being observed [51]. Gabapentin is an effective drug for anxiety in non-cancer patients and has shown promising results (300 mg dose is most effective) in a controlled trial with breast cancer survivors [52].

Cognitive Disorders (Cancer-Related Cognitive Impairment)

Cognitive functioning refers to mental processes such as attention, perception, thinking, reasoning, and remembering. Intact cognitive functioning is important, as it enables a person to function autonomously within society. Cognitive symptoms or cancer-related cognitive impairment (CRCI) have been mainly studied in patients with non-CNS cancers after systemic treatment (chemotherapy). In patients with brain tumor/brain metastases, the presence of the malignancy itself, treatment (e.g., surgery, radiotherapy, systemic treatment), and recurrence threaten cognitive functioning. Over 90% of brain tumor patients show cognitive impairment during their disease course [53].

Symptoms consist of attentional deficits, reduction of short-term and working memory, executive functions and/or processing speed [54–57]. Breast cancer survivors report cognitive symptoms in ~50%, while only 15–25% have measurable cognitive impairment [55, 58]. Psychological comorbidities may additionally play a crucial role between subjective and objective experience of cognitive symptoms [59]. Besides cognitive impairment by chemotherapy, hormone therapies in breast cancer (e.g., aromatase inhibitors, selective estrogen receptor modulators, ovarian function suppression) and androgen deprivation therapy in prostate cancer (e.g., luteinizing hormone-releasing hormone, enzalutamide) may influence cognitive functioning. Targeted therapies, such as antiangiogenics in renal cell cancer (e.g., Sunitinib, Pazopanib, etc.), can induce cognitive deficits. Studies on cognitive impairment with immunotherapy such as anti-CTLA-4-inhibitors (e.g., Ipilimumab) or checkpoint-inhibitors (e.g., Nivolumab, Pembrolizumab, Atezolizumab, etc.) are lacking so far, but animal models have found interactions between brain function and immunotherapy. As these specific agents have a major impact on survival, long-term toxic effects on cognitive function are crucial in terms of quality of life (QoL). To date it is unclear whether CRCI results from cancer itself, treatment and/or

Table 10.3 Neuropsychological measures recommended by the international cancer and cognition task force (ICCTF) [61]

Main measures	Domains assessed
Hopkins Verbal Learning Test-Revised (HVLT-R)	Verbal memory, delayed recall
Controlled Oral Word Association Test (COWA)	Speeded lexical fluency, executive function
Trail Making Test (TMT)	Psychomotor speed, executive function
Additional measures	**Domains assessed**
Auditory Consonant Trigrams	Working memory, executive function, complex attention
Letter-Number Sequencing (WAIS)	
Paced Auditory Serial Addition Test (PASAT)	
Brief test of attention	

psychological comorbidities. Some studies suggest that other factors, e.g., age, psychosocial status, and genetic susceptibility can predispose to a higher risk of CRCI [60].

The negative impact of CRCI on QoL (social relationships, self-confidence, autonomy, return to work) is an important issue in cancer survivors and has led to a "CRCI: state of the art, detection, and management strategies in cancer survivors"—consensus paper from the European Society for Medical Oncology (ESMO) in 2019 [61].

Diagnostic work-up (Table 10.3): The International Cancer and Cognition Task Force (ICCTF) recommends neuropsychological testing to assess various domains of cognition. Definition of cognitive impairment according to ICCTF consists of ≥2 test scores ≤ −1.5 standard deviations from the normative mean (or an appropriate control group) or 1 test score ≤ −2.0 standard deviations [56]. Assessment of cognitive difficulties should be done with validated tests such as the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog). The FACT-Cog is a subjective neuropsychological instrument especially designed for cancer patients and can be used as a screening tool to assess the necessity for further neuropsychological testing [56].

Subjective cognitive complaints and objective performance on neuropsychological tests rarely correlate very highly [62]. Psychological influences such as depression, anxiety [62, 63] fatigue, or insomnia [64] often influence subjective cognitive difficulties [65]. Consequently, psychological comorbidities (see sections above) should also be assessed [63].

ICTTF recommends using cognitive tests with adequate sensitivity to assess the different cognitive domains mostly impaired in cancer survivors such as the Trail Making Test (psychomotor speed and executive function), Hopkins Verbal Learning Test (verbal memory and delayed recall), Controlled Oral Word Association Test (speeded lexical fluency and executive function). Additional tests are the Auditory Consonant Trigrams, Letter-Number Sequencing, Paced Auditory Serial Addition Test, and Brief test of attention [56].

Imaging studies with cMRI/functional MRI, conducted mainly after conventional systemic chemotherapy, reported reductions in grey matter volume/density, reductions in white matter microstructure, changes in brain activation and neuronal connectivity [66]. Functional hyperactivation/hyperconnectivity of brain regions involved in cognition pattern are thought to be compensatory processes for treatment-induced brain injury [67, 68]. Brain imaging should not be used to diagnose CRCI, but can be useful to exclude the differential diagnosis (e.g., brain metastases, cerebral bleeding, or infection).

Differential diagnosis in patients with cognitive impairment can be difficult in cancer survivors because some of the symptoms overlap with other problems reported (e.g., depression and anxiety, cancer-related fatigue, sleep disturbances, treatment side effects, substance abuse, etc.). Other medical conditions such as hypothyroidism and vitamin B12 deficiency should be ruled out. A complete blood count with differential and metabolic panel to screen for anemia, kidney or liver failure, electrolyte disturbances, infection, and vitamin D deficiency should be conducted [61].

Treatment of CRCI consists of non-pharmacological and pharmacological treatment. Of course, underlying medical conditions (e.g., hypothyroidism, anemia, etc.) should be treated specifically [61].

A non-pharmacological treatment option is a physical activity. In breast cancer patients a 12 week exercise program improved cognitive outcomes. Other studies showed comparable results (physical exercises or yoga), but without objective assessment of cognitive functioning. Behavioral interventions such as education, cognitive behavior therapy, or cognitive training/rehabilitation are helpful. Cognitive behavior interventions in cancer survivors report improvement in CRCI with variable results in objective cognitive tests [69].

Pharmacological treatment options are scarce. No evidence exists to support the use of agents, such as erythropoietin or methylphenidate in CRCI [54]. Clinical trials with diverse neurostimulation, neuroprotectants, or antineuroinflammatory agents are currently ongoing. The main objective of these trials is the prevention of CRCI during cancer treatment. Efficacy of other neurostimulants (e.g., caffeine or modafinil) and anti-dementia drugs (e.g., donepezil, memantine) is very limited [70].

Pain and Peripheral Neuropathy

Pain is a common symptom in cancer survivors. The International Association for the Study of Pain (IASP) defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage [71]. Cancer-related pain can be categorized as tumor-related, treatment-related, or pain unrelated to cancer itself (e.g., chronic back pain, osteoarthritis, chronic headache, etc.). We will mainly focus on treatment-related cancer pain [72] (Table 10.4).

Table 10.4 Chronic pain syndromes related to cancer treatment [72]

Surgery
Post-thoracotomy pain, Intercostal neuralgia
Lymphedema, Neuroma pain
Pain related to breast implants/reconstruction
Phantom pain, Postmastectomy pain
Postsurgical neck dissection pain
Radiation
Chest pain/tightness, Cystitis
Enteritis/proctitis, Fibrosis of skin or myofascia
Fistula formation, Myelopathy
Osteoradionecrosis, Pelvic insufficiency fractures
Peripheral nerve entrapment, Plexopathies
Gl, abdominal, other adhesions in the radiation field
Hormonal therapy
Arthralgia/myalgia, Muscle cramps/spasms
Carpal tunnel syndrome
Chemotherapy
Arthralgia/myalgia, Osteoporosis
Osteonecrosis, Chemotherapy-induced peripheral neuropathy
Muscle cramps
Steroids
Osteoporosis, Osteonecrosis (avascular necrosis, typically femoral head, knee, humeral head)
Antiresorptive treatment
Osteonecrosis of jaw
Hematopoietic stem cell transplantation (chronic graft-versus-host disease)
Abdominal, GI adhesions, pain
Arthralgia/myalgia
Contractures with pain and decreased range of motion
Corneal ulcerations with pain, dryness, and burning eyes
Cystitis, Erythema
Esophageal strictures and ulcers leading to retrosternal pain
Fibrosis/scleroderma with contractures, pain, and decreased range of motion
Infection, Inflammation/edema
Mucous membrane inflammation, thinning, strictures, ulcers (mouth, GI tract, vagina)
Muscle cramps, Peripheral neuropathy, Osteonecrosis of joints

Prevalence of chronic pain in cancer survivors is estimated up to 40%, but importantly the timing of pain assessment needs to be considered, as treatment-related pain reduces over time (tissue regeneration and healing). Factors that influence pain are type and stage of underlying cancer, anticancer treatment modalities (e.g., surgery, chemotherapy, radiotherapy, etc.), time since completing specific therapy and comorbidities. Additionally, sex/racial disparities and psychosocial background have impacts on chronic pain in cancer survivors [73].

Surgery is often responsible for persistent pain (e.g., postmastectomy pain or phantom limb syndrome) in cancer survivors. Additional risk factors are linked to inadequate postoperative pain management, postoperative (adjuvant) radiotherapy, neurotoxic systemic therapy, and psychological comorbidities such as anxiety,

depression, and fear of recurrence [74–76]. Although less invasive surgical procedures are being applied nowadays, postsurgical pain is still frequent. Lumpectomy and axillary dissection can result in more pain than standard modified radical mastectomy. Chronic postoperative pain can result as common surgical complications from fistulae, abdominal collections, adhesions, lymphoedema, etc. [77, 78].

Radiotherapy (RT) can mainly induce osteoradionecrosis, plexopathies, or skin fibrosis resulting in chronic pain [79]. They are time-dependent and mostly occur late after radiation therapy. With new RT techniques (e.g., Image-guided RT, Intensity-modulated RT, stereotactic RT), incidence of radiation-induced pain may be reduced in future [80].

Hormonal therapy like aromatase inhibitors used in breast cancer can induce arthralgias with joint pain or/and stiffness in almost 40% of cases, mostly occuring within the first 3 months [81, 82]. Other symptoms related to hormonal therapy (estrogen deprivation) is vaginal dryness leading to dyspareunia (painful intercourse) [80]. The prevalence of osteoporotic fractures under hormonal therapy (estrogen deprivation, androgen deprivation) and prolonged use of corticosteroids (with additional risk of osteonecrosis) is significantly elevated and can lead to acute and chronic pain in cancer survivors.

Chronic graft-versus-host disease (GvHD) and GvHD treatment after hematopoietic cell transplantation may induce chronic pain [83].

Treatment of chronic pain in cancer survivors consists of a multidisciplinary approach and a combination of analgesics, physical therapy, physical activity, and psychosocial interventions. Complementary and alternative treatment modalities may be useful [80, 84] (Table 10.5).

Pharmacological options are mainly classical analgesics (nonopioid agents) such as nonsteroidal antirheumatic drugs (NSAIDs), metamizole (when available), paracetamol (acetaminophen), and low or high potency opioids as in chronic non-cancer patients [84, 85]. Co-analgesics like antidepressants and anticonvulsants act mainly on persistent neuropathic pain (e.g., CIPN, postherpetic neuropathy). Opioids are indicated in patients with moderate to severe pain, unresponsive to non-opioids. Although most oncologists should be familiar in treating patients with opioids in the advanced stage (palliative setting), there are two main differences. First, breakthrough pain (sudden and brief flare-up of pain) does seldom occur in cancer survivors therefore rescue doses of immediate-release opioids are not indicated. Second, fast dose escalations and high doses of opioids are seldom needed because of the chronic characteristics of pain. Extended-release opioids with oral administration when possible in a time-scheduled manner are preferred. Whenever possible, combination with nonopioids and/or co-analgesics if indicated is reasonable [86].

Non-pharmacological approaches are based on physical medicine and rehabilitation. Physical therapy (PT) and related approaches such as progressive resistance training, myofascial release, visceral therapy, neuromuscular reeducation, or craniosacral manipulation are the most common treatment modalities [80]. E.g., PT

Table 10.5 Chronic pain management in cancer survivors [72]

1.	**Definition of health care provider responsible for pain management and prescribing** e.g., Medical or radiation oncologist, primary care provider, chronic pain specialist Opioids should be prescribed by only ONE provider!
2.	**Evaluation** Comprehensive history and physical examination with attention to functional and psychosocial issues related to pain If opioids considered, standard opioid risk assessment tool may be useful (e.g., Screener and Opioid Assessment for Patients with Pain or Opioid Risk Tool) New/changing pain syndromes: exclude recurrence or second primary, development of late effects of treatment – consider imaging or further investigations as needed
3.	**Management** *Pharmacologic* Co-analgesics: antidepressants, anticonvulsants, nonsteroidal anti-inflammatory drugs, acetaminophen/paracetamol, metamizole (if available) Morphine or other opioids, e.g., Tramadol, Tilidin, Hydromorphone, Oxycodone, Fentanyl, Buprenorphine, etc. – Establishment of functional goals to guide dose titration – Maintenance of ongoing monitoring for opioid misuse, abuse, or diversion – Management of emerging problems consistent with medical best practices and existing laws and regulations *Non-pharmacologic* Exercise program Physical medicine and rehabilitation, physical therapy, transcutaneous electrical nerve stimulation, scrambler therapy Cognitive-behavioral therapy Integrative medicine approaches (acupuncture, massage) Interventional approaches

may reduce pain and improve shoulder function and secondary QoL after axillary dissection in breast cancer patients [87].

Increasing blood flow, relieving muscle spasms, and reducing inflammation are probably the key effects of PT. Superficial heat with heating pads, deep heat with ultrasound, or cryotherapy can be used. Kinesio-taping (K-taping) is a valuable option in neuromuscular dysfunction and lymphedema [88, 89].

Orthotics are helpful in the management of skeletal or neurologic disabilities leading to chronic pain syndromes [80].

Chemotherapy-Induced Peripheral Neuropathy

Chemotherapy-induced peripheral neuropathy (CIPN) is defined as a progressive, enduring, and often partial reversible or irreversible condition featuring pain, numbness, tingling, and sensitivity to cold in the hands and feet (sometimes progressing to the arms and legs). CIPN after curative systemic treatment is very common in cancer survivors. Cytotoxic drugs leading to CIPN are mainly taxanes, platinum salts, vinca alkaloids, eribulin, and proteasome inhibitors [80] (Table 10.6).

Table 10.6 Agents associated with chemotherapy-induced peripheral neuropathy (CIPN) [80]

Chemotherapy class	Example drugs	Incidence (%)	Comments
Vincaloids	Vincristine Vinblastine Vinorelbine Vindesine	30–57 25–40 7–40	Typically sensorimotor neuropathy, autonomic features in 20–30%. Dose-dependent. Coasting (worsening symptoms weeks/months after the last dose of chemotherapy) possible. May resolve within 3 months, often irreversible with vincristine
Platinum compounds	Cisplatin Carboplatin Oxaliplatin	30–100 6–42 7–20	Sensory or sensorimotor neuropathy, autonomic features less common, risk of ototoxicity. Dose-dependent. Coasting common
Taxanes	Paclitaxel Nab-Paclitaxel Docetaxel	57–83 73 overall; 10–15 severe 11–64 overall; 3–14 severe	Painful symmetrical distal sensory neuropathy. Motor effects less common. Nab-Paclitaxel neuropathy often less severe. Symptoms may alternate. May ascend limbs. Cumulative, dose-dependent. Coasting common
Proteasome inhibitors	Bortezomib	31–55 overall; 9–22 severe; less if given s.c.	Small fiber sensory neuropathy. Motor and autonomic features common. Dose-dependent. May resolve within 3–6 months but may persist
Other	Thalidomide	25–83 overall; 15–28 severe	Sensory or sensorimotor neuropathy, with autonomic features in 56%
	Lenalidomide	10–23 overall; 1–3 severe	Dose-dependent. Persists for 1 year or longer. Similar to thalidomide
	Etoposide	1–2	Sensorimotor polyneuropathy with autonomic dysfunction
	Cytarabine	Rare	Severe sensorimotor neuropathy, greater risk with high dose or in combination with daunorubicin or asparaginase. High dose: acute irreversible cerebellar syndrome
	Ifosfamide	8	Neuropathy

Therapy-associated risk factors of developing CIPN depend on the individual antineoplastic drug, cumulative doses, duration of exposure, scheduling, and combined therapies [90]. Patient-associated risk factors are mainly older age (>75 years) and diabetes mellitus [91]. Preexisting neuropathy and concomitant diseases such as chronic alcohol abuse, renal insufficiency, hypothyroidism, VitB12 deficiency, chronic infections, or autoimmune diseases have a higher likelihood of developing/worsening neuropathy [92–94]. Smoking habits and genetic susceptibility may be additional risk factors [95, 96].

The pathophysiology of CIPN consists of toxic effects from antineoplastic agents to large sensory nerves leading to sensory axonal neuropathy, sometimes involving motor and autonomic nerve fibers. Damage of dorsal root ganglions leading to ganglionopathy (often irreversible) or small fiber neuropathy with the affection of nerve

terminals for pain and temperature perception may be found. Depending on the cytotoxic compound, these different nerve involvements in CIPN will eventually lead to diverse clinical symptoms (see Table 10.6) [80, 97].

Diagnostic work-up (Fig. 10.1): Early recognition of CIPN during systemic treatment with abovementioned agents is crucial for adequate management. Neurological evaluation at baseline to detect preexisting neuropathy and before every cycle is mandatory to avoid irreversible neuropathy [97, 98]. Biomarkers for early detection or monitoring of CIPN do not yet exist, although there are ongoing studies with the measurement of serum neurofilament light [99].

Neurophysiological examination with electromyography (EMG) and determination of nerve conduction velocity can provide additional information, both at baseline and during therapy. However, objective parameters often do not correlate with

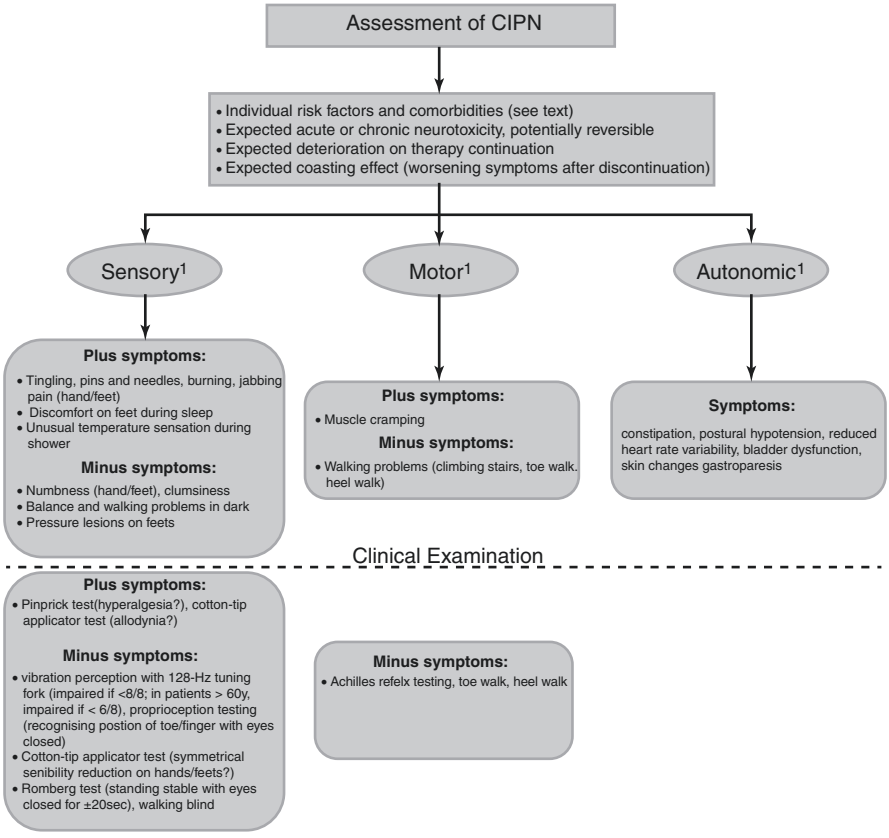

Fig. 10.1 Practical work-up of CIPN adopted from [97]. *CIPN* chemotherapy-induced peripheral neuropathy. (1) In asymmetric sensory/motor symptoms or normal clinical examination in symptomatic patients consider neurophysiology testing. Small fiber neuropathy may show normal neurophysiology. (2) If suspicion of autonomic neuropathy, neurophysiology testing of sympathetic skin response and heart rate variability should be considered

subjective symptoms of the patient; therefore, neurophysiological monitoring during/after treatment is not recommended. Sometimes somatosensory potentials can be useful to detect affection of proximal sensitive nerves or to exclude rare neurologic comorbidities. EMG rarely provides further information and is usually not needed in clinical routine. Small fiber neuropathy may show normal neurophysiological examination and can only be detected on skin biopsy [97].

Grading of CIPN with clinician-reported outcome measurements (CROMs) is standard. The most utilized assessment tool is the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) ranging from asymptomatic (Grade 1), to moderate symptoms, limiting instrumental activity of daily living (ADL) (Grade 2), to severe symptoms, limiting self-care ADL (Grade 3), to life-threatening consequences, with urgent interventions needed (Grade 4) [100].

Prevention of CIPN (Table 10.7): to date, there is no pharmacological agent having the potential to prevent CIPN. The ESMO-EONS-EANO Clinical Practice Guidelines on systemic therapy-induced peripheral and central neurotoxicity recommend against several agents [97].

Cryotherapy with frozen socks or gloves (most evident in taxane-based therapy) as a non-pharmacological prevention tool can be considered. However, study results are heterogenous [97, 101, 102]. Compression therapy with surgical gloves may lead to a subjective reduction of neuropathy (treatment with nab-Paclitaxel) [103]. A protective effect is seen with exercise and functional training (e.g., Exercise for

Table 10.7 Chemotherapy-induced peripheral neuropathy (CIPN) prevention measures [97]

Intervention	Comment (study compound)
Pharmacological prevention (not recommended)	
Acetylcysteine	Oxaliplatin-based ChT
Alpha-lipoic acid	Platinum-based ChT
Amifostine	Platinum- and taxane-based ChT
Amitriptyline	Vinca alkaloids, platinum-based, or taxanes
Calcium/magnesium	Exclusively oxaliplatin-based ChT
Carbamazepine	Oxaliplatin-based ChT
MR309, selective sigma-1 Receptor antagonist	One positive randomized phase II study (potential neuroprotective)
Omega-3 fatty acids	Taxane-based, potentially positive outcome but not enough evidence to support the use
Vitamin B	Taxane-, oxaliplatin- or vincristine-based ChT
Vitamin E	Platinum- and taxane-based ChT
Multivitamin use	
Non-pharmacological intervention (can be recommended)	
Acupuncture	Electroacupuncture worse than sham acupuncture
Exercise	Possible protective effect of exercise on CIPN
Compression therapy with surgical gloves	One study, additional drugs such as duloxetine were allowed
Cryotherapy frozen socks and gloves	With taxane therapy

ChT chemotherapy

Table 10.8 CIPN therapy: pharmacological interventions [97]

Intervention	Comments	Recommended dose
Selective Serotonin Reuptake Inhibitors (SSRI)		
Duloxetine	Reduction of neuropathic pain (plus symptoms)	30 mg/day for 1 week, then 60 mg/day
Venlafaxine	Reduction of acute and chronic neuropathic pain (oxaliplatin-treated patients)	50 mg initially, followed by 37.5 mg twice/day
Anticonvulsants		
Gabapentin	Efficacy in non-CIPN neuropathic pain only	Targeted dose: 2700 mg/day; dosing in non-CIPN studies: 1200–3600 mg/day
Pregabalin	Efficacy in non-CIPN neuropathic pain only	Targeted dose: 300 mg twice/day
Tricyclic antidepressants		
Amitriptyline	Small improvement of CIPN, trend for improvement of QoL	Starting dose: 10 or 25 mg/day Targeted dose: 50 mg/day
Nortriptyline	Small improvement of CIPN	Targeted maximum dose: 100 mg/day
Opioids		
Tramadol	Efficacy in non-CIPN neuropathic pain only, additionally serotonin-noradrenaline reuptake inhibitor	Tramadol 200–400 mg in two (extended release) or three doses
Strong opioids	Efficacy in non-CIPN neuropathic pain only	Smallest effective dose
Topical local intervention		
Topical low-concentration menthol cream	improvement in pain scores after 4–6 weeks	1% menthol creme twice/day to affected area and corresponding dermatomal region of spine
Topical baclofen, amitriptyline, ketamine gel	Effect after 4 weeks on CIPN 20, especially on motor subscale	10 mg baclofen, 40 mg amitriptyline, and 20 mg ketamine
Capsaicin-containing patches, 8%	Efficacy in non-CIPN neuropathic pain mostly, small study in CIPN	Application 30 min on the affected region for 60 min, effect lasting 90 days

Cancer Patients, self-management exercise interventions) to improve sensorimotor functions and muscle strength [104].

Treatment options: Pharmacological treatment options (Table 10.8) mainly focus on the reduction of neuropathic pain (plus symptoms). Symptoms like numbness or clumsiness (minus symptoms) are not influenced by pharmacological interventions. Psychosocial comorbidities (depression, anxiety, sleep disturbances) can aggravate neuropathic pain and should be assessed [97].

Selective serotonin reuptake inhibitor (SSRI): Duloxetine is recommended for the treatment of neuropathic pain starting with 30 mg in week 1 and increasing to 60 mg in week 2 [105]. Venlafaxine has shown efficacy in a small study and can be considered as a treatment option for neuropathic pain [106].

Table 10.9 CIPN therapy: non-pharmacological interventions [97]

Intervention	Comments
Acupuncture	Several small studies positive
Neurofeedback	Potential benefit for EEG-based neurofeedback
Physical exercise	Several strategies are available: supervised medical exercise (sensorimotor function, endurance, strength of flexibility), self-management interventions
Scrambler therapy	Noninvasive cutaneous electrostimulation
Self-guided online cognitive behavioral strategies	
Spinal cord stimulation	Option refractory pain due to CIPN, invasive procedure: electrode insertion into dorsal reentry zone of spinal cord with pulse generator implantation under skin

Anticonvulsants and tricylic antidepressants (TCAs): The efficacy of anticonvulsants and TCAs in CIPN is less clear. Since there is good evidence in treating general neuropathy with these agents, they may be beneficial in CIPN. Of note, the onset of action can take up to 2 weeks, but adverse effects may occur immediately; therefore inform the patient [97].

Tramadol (double mechanism of action: opioid and serotonin-noradrenaline reuptake inhibitor) or strong opioids can be used as adjunction or salvage treatment for neuropathic pain, although data are lacking in CIPN.

NSAIDs or glucocorticoids are not recommended in CIPN [107].

Topical treatment interventions such as menthol creme 1% [108] or capsaicin 8% patches [109] have shown reduction in CIPN mainly related to small fiber neuropathy. Topical treatment with a baclofen/amitriptyline and ketamine-containing gel could be used in some cases.

Non-pharmacological treatment options (Table 10.9) are physical exercise, including vibration therapy and training to improve coordination, sensorimotor and fine motor function, acupuncture, cognitive and behaviorally based pain management interventions (PROSPECT), and spinal cord stimulation (only in selected patients, with refractory neuropathic pain). Neurofeedback could be an option for some patients [97].

Aids and supply tools to support activities of daily living should be discussed with cancer survivors, depending on the degree of disability from CIPN [97].

Mucosal, Dental, and Soft Tissue Problems of the Head and Neck

Treatment modalities such as surgery, chemotherapy, and radiation therapy may directly or indirectly induce damage to the soft tissue of the head and neck. Especially in patients after head and neck cancer (HNC) oral complications are

relevant. Surgery can cause mutilation and result in physiologic changes. Radiation therapy is often complicated by mucositis, persistent dysphagia, hyposalivation, and dental issues and may lead to osteoradionecrosis. Persistent taste changes or mucositis can be seen after curative chemotherapy [110].

Dysphagia: The prevalence of dysphagia and dysphagia-related diagnoses (e.g., esophageal stricture, aspiration pneumonia) has a high prevalence in HNC cancer survivors, with the highest prevalence after multimodality therapy (e.g., chemoradiation, surgery, and adjuvant therapy) [110]. Fiberoptic endoscopic evaluation of swallowing is needed to exclude local problems (e.g., local recurrence) and gastroscopy might be indicated if esophageal dysphagia is suspected. Therapeutic options are swallowing exercises, use of semisolid food, or food supplementation. In cases of complete persistent dysphagia percutaneous endoscopic gastrostomy (PEG) or parenteral nutrition should be considered [111].

Voice and speech: The voice is a commonly affected domain notably in HNC cancer survivors, due to radiotherapy-induced fibrosis, cranial neuropathies, or scarring secondary to surgical intervention and can lead to lower QoL during survivorship. Voice therapy and rehabilitation are strategies for improving voice outcomes, and studies have shown improvements in voice quality and function leading to an increase of QoL after voice rehabilitation [112, 113].

Xerostomia and oral health: Xerostomia is the subjective complaint of dry mouth that usually reflects a decreased presence of saliva [114]. Diminished saliva results in dental demineralization and caries, and increases the risk of oral infections (e.g., oral candidiasis). Additionally, it can lead to tongue fissures, dysgeusia, voice problems, halitosis, oral soreness, inability to wear dentures, and dysphagia with the result of a decreased QoL [115, 116]. Radiation therapy to the head and neck involving salivary glands commonly leads to chronic salivary gland dysfunction. Furthermore, chronic GvHD after allogeneic stem cell transplant can cause xerostomia. Xerostomia may be exacerbated by concomitant medication (e.g., anxiolytic medication, antidepressants, antihypertensive, or opioids) [117].

Oral hygiene including brushing (twice a day) and flossing will prevent infection and support dental integrity. Early dental interventions are mandatory when indicated. Daily administration of fluoride gels may be useful.

Maintaining hydration with tap water is encouraged. Milk is thought to overcome xerostomia as it moisturizes, buffers acids, and can lead to dental remineralization through its calcium and phosphate content [118]. Caffeine and tobacco smoking can lead to a reduction in saliva production and should be reduced [119]. Stimulation of the salivary glands through mastication may be helpful (e.g., chewing xylitol gum or sugar-free candies) [118].

Salivary substitutes (application by rinses, swab sticks, gels, sprays, etc.) may provide temporary relief of discomfort. Systemic sialogogues such as pilocarpine hydrochloride, a nonspecific muscarinic agonist (5 mg three times a day) if supportive therapy is not sufficient can be used [120]. Cevimeline, a selective M3 muscarinic receptor acetylcholine analog (30 mg three times a day) increases non-stimulated salivary flow [121, 122]. Contraindications such as uncontrolled asthma or narrow angle glaucoma need to be considered for both agents. Bethanechol (25 mg three

times a day) a cholinergic stimulant is another option. Sialogogues usually have limited effects in patients with severe salivary dysfunction though. Hyperbaric oxygen to improve angiogenesis and fibroplasia in nonhealing tissue, acupuncture, and salivary gland tissue transplantation are additional options in refractory xerostomia. In chronic GvHD-related xerostomia additional treatment with immunosuppressive therapy such as steroids and cyclosporines is mostly needed [117].

Osteoradionecrosis (ORN) and osteonecrosis of the jaw (ONJ): ORN of the jaws is mostly a delayed bone reaction caused by the failure of bone healing following radiation therapy [123]. ONJ is induced by osteoprotective treatment with bisphosphonates or denosumab (RANKL-inhibitor) and the pathophysiology is complex. Complications such as pathologic fractures and oral fistula are feared complications in both entities with debilitating outcome and reduced QoL [124].

Managing ORN and ONJ constitutes of reducing comorbid factors such as optimizing oral hygiene, controlling oral infections, nutritional support, removal of devitalized tissue (sequestrectomy), and symptomatic treatment (e.g., pain management) [125, 126]. Hyperbaric oxygen combined with limited surgery has shown promising results in ORN [127–129]. Additionally, pentoxifylline in combination with vitamin E has been associated with positive results [130]. Surgical interventions consist of sequestrectomy and bone recontouring/smoothing. In refractory patients, microvascular surgical techniques and tissue transfer can be provided if feasible [129].

Taste disorders: Taste disorders are commonly encountered in cancer survivors, notably in patients with HNC following surgery, radiation therapy, or chemotherapy [131, 132]. Persisting taste loss may be caused by direct damage to taste receptors from chemotherapy or radiation therapy [133, 134] and secondary to xerostomia. Chronic GvHD has also been associated with taste reduction and taste change [135, 136]. Assessment of taste should begin with a past medical history including alcohol abuse and tobacco smoking. Association of the symptoms following the use of medication or nutritional supplements. A clinical examination of the oral cavity and head/neck is conducted, including assessment of salivary gland function plus olfactory and taste testing [137, 138].

Management should consist of treating reversible causes. Supportive measures applicable to all patients, independently of the underlying cause, such as chewing gum or candy to mask unpleasant taste can be offered [139]. Treatment of xerostomia or antibiotic use if indicated may improve taste complaints. Zinc supplements may be considered in patients with persistent taste impairment [140]. Dronabinol (tetrahydrocannabinol) has been reported to improve taste in some patients [141].

Recurrent or secondary cancer: Patients at highest risk of oral or head and neck cancers are those with prior HNC. Continuation of tobacco smoking and high alcohol consumption increases the risk. Additionally, cancer survivors following upper aerodigestive tract cancer or under chronic immunosuppression following HCT need to be followed carefully for HNC [142].

Systemic consequences of poor oral health: Poor oral conditions can lead to systemic health problems due to altered/reduced nutrient, caloric, vitamin, and mineral intake and may consequently contribute to persistent fatigue, depression, or

cardiovascular events. Consequently, higher mortality rates are seen in these patients, initially cured of their tumors [143]. Radiation therapy to the head and neck may lead to hypothyroidism and regular follow-up of thyroid function (TSH measurement once a year) is necessary [144].

Cancer-Related Lymphedema

Lymphedema (LE) is defined as an incurable medical condition caused by lymphatic fluid retention resulting in tissue swelling. Cancer itself and cancer treatment modalities such as surgery (e.g., axillary lymph node dissection in breast cancer) and radiation therapy (e.g., radiation to pelvic lymph node stations in cervical cancer) can damage lymph drainage routes leading to accumulation of lymph fluid in the interstitial tissue of corresponding limbs or body areas or secondary LE [145]. Symptomatic LE can result in discomfort, heaviness, reduced mobility, and pain, affecting quality of life (QoL) in cancer survivors [146]. LE can increase distress, depression, and anxiety, especially in regard to body image [147]. Because of ongoing improvement in cancer treatment, the prevalence of LE in cancer survivors will increase in future years.

Cancer-related LE can occur in any type of cancer with involvement of lymph nodes (e.g., skin, urologic, gynecologic, gastrointestinal, head and neck, etc.) Incidence of LE in breast cancer survivors, for example, ranges from 13 to 65% depending on definition [148].

Known risk factors for LE, mostly studied in breast cancer patients, are overweight and obesity. Furthermore, postoperative infection, adjuvant radiation therapy, and complete lymph node dissection increase the risk. Other medical conditions such as diabetes, COPD, hypertension, or hypothyroidism might be related to an increased risk of LE. Data do not support that LE risk can be reduced by avoiding blood draws, injections, or blood pressure measurements on the affected limb [148].

Diagnostic work-up: There is no standardized definition of LE. The most common method to prove swelling of an affected limb is tape measurement. A difference of 2 cm between affected and non-affected limb is considered as cutoff [149]. This is not true for swelling of a body area (e.g., on the trunk) or for LE only causing heaviness or pain. Patient history and physical examination are mandatory to assess LE, followed by measuring limb volume, usually in comparison to the non-affected limb [148].

Instrumental measurement of limb volume can be done by water displacement (once considered as gold standard) [150], lymphoscintigraphy [151], perometry [152], or bioimpedance [153]. With lymphoscintigraphy, lymph transport capacity can be estimated accurately. Perometry uses infrared beams to measure limb volume [152]. The newest option of assessing limb volume is bioimpedance. With this method even subclinical swelling can be identified [153].

Most clinicians assess LE by self-reported (subjective) symptoms such as swelling, pain, or heaviness, but self-report and instrumental measurements have only moderate correlations [148].

Differential diagnosis: Local recurrence of underlying cancer and deep vein thrombosis should be ruled out, especially with acute onset or association with other clinical symptoms. History and clinical examination followed by ultrasound with duplex sonography or CT scan might be then indicated.

Treatment options: Lymphedema is not curable and management should focus on reducing limb volume, complications such as infection and maintaining/improving limb function and quality of life. Early detection and increased awareness are important to reduce LE risk and severity [154].

Complex physical therapy, low-level laser therapy (LLLT), pharmacological treatment, or surgery are options to consider. Complex physical therapy (with complete decongestive therapy) includes multilayer bandaging (MLB), exercise, non-elastic wrapping, use of compression garments, and topical skincare. Importantly, compression garments should be customized to fit properly and need to be replaced regularly (every 3–6 months).

LLLT is effective in reducing limb size, extracellular fluid, and tissue stiffness in patients with breast cancer. At least two cycles are required [148].

Pharmacological options are scarce. There is no indication for diuretics. The trace element selenium is a nontoxic anti-inflammatory agent with some effects on LE [155]. One study reported a significant reduction of swelling in patients with head and neck cancer after curative surgery and bilateral neck dissection [156].

Surgical options such as microsurgery with anastomosis of lymph vessels (reconstructive lymphatic microsurgery) or resection of lymphedematous tissue are mostly restricted to patients where other options have failed to improve LE [157]. In one study with cancer and non-cancer-related LE, reduction of limb size could be reduced in up to 83% of patients with surgical intervention [158].

Dermatologic Toxicity

Cutaneous toxicities are important to address, because of their high frequency and visibility in cancer survivors, leading to significant physical and psychosocial discomfort [159–161]. Notably, radiation therapy and novel anticancer agents (e.g., anti-EGFR-targeting, immunotherapy, BRAF-Inhibition), causing acute and chronic adverse reactions involving the skin [161]. The skin and its appendages are high-turnover tissues with epithelial, connective tissue, vascular, and neural components all of which explain the high frequency of toxic effects from systemic or local treatment [162].

Acneiform rash: papulopustular eruption (acneiform rash) is characterized by an eruption consisting of papules and pustules typically appearing in the face, scalp, and upper chest and back. The appearance of erythematous papules or pustules is a common presentation with many agents, most notably those targeting the epidermal growth factor receptor (EGFR), including small-molecule receptor tyrosine kinase inhibitors (TKIs) used as adjuvant therapy in cancer such as osimertinib (lung cancer) or monoclonal antibodies such as pertuzumab (breast cancer). Inhibitors of the EGFR downstream kinase, mitogen-activated protein kinase inhibitors (MEKis),

such as cobimetinib (adjuvant treatment in melanoma), are also associated with the development of papulopustular eruption. An inflammatory mechanism underlies this reaction, likely a consequence of altered keratinocyte proliferation, differentiation, migration, and chemokine expression [160]. Preventive measures should include avoiding frequent washing with hot water, skin irritants, such as solvents or disinfectants, and avoiding excessive sun exposure. Skincare measures constitute of alcohol-free skin moisturizers at least twice daily, preferably with urea-containing (5–10%) moisturizers and sun protection products (sun protection factor >15). Pharmacologic prophylaxis with topical (topical Metronidazole) and oral antibiotics with anti-inflammatory activity like tetracyclines (e.g., doxycycline, minocycline) can reduce the incidence of acneiform rash. The use of concomitant topical steroids as prophylaxis can be done, but data are controversial. Treatment of acneiform rash consists of oral tetracyclines and higher potency topical steroids for 6 weeks in grade 1 and 2 rash. For grade 3 and 4 oral steroids (e.g., prednisone 0.5–1 mg/kg for 7 days and weaning over 4–6 weeks) and pausing the responsible agent until reduction to grade ≤1. When bacterial superinfection is suspected bacterial culture should be obtained and antibiotic treatment for at least 14 days is indicated. In refractory cases, the use of oral retinoids or dapsone could be considered. Concomitant use of tetracyclines and oral retinoids are contraindicated, because of the risk of pseudotumor cerebri [163].

Immunotherapy-related skin changes: Since immunotherapy, especially immune checkpoint-inhibitors (CPI) such as PD-1/PD-L1-inhibitors (e.g., Pembrolizumab, Durvalumab) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-inhibitors (e.g., Ipilimumab) are emerging therapies in the adjuvant setting (e.g., locally advanced melanoma or lung cancer), potential cutaneous side effects should be discussed here. Dermatologic adverse events are among the most common side effects related to immunotherapy [164, 165]. Rashes from CPI are mostly maculopapular or morbilliform and pruritic [166] Grades 1–2 rashes (skin involvement <30% of body surface area) with mild pruritus may be treated with topical steroids and oral antihistamines. Immunotherapy can be continued in these cases. Grade 3 (skin involvement >30% of body surface area) usually requires systemic steroids while temporary discontinuation of immunotherapy until improvement to < grade 2. Grade 4 reactions (life-threatening superinfection; Stevens-Johnson syndrome, toxic epidermal necrolysis, or bullous dermatitis covering >30% of body surface area, leading to admission to ICU) typically require high-dose systemic steroids and permanent discontinuation of immunotherapy [167].

Hyperpigmentation: Antimetabolites, especially 5-FU or bleomycin, are known to cause reticulate hyperpigmentation or melanonchia. This hyperpigmentation may persist for a certain time, even if the drug is discontinued and may increase in intensity after sun exposure [168, 169].

Connective Tissue Abnormalities: Scleroderma-like reactions (e.g., skin tightening, contractures of knees or fingers) were reported to occur in patients receiving taxanes. Docetaxel and paclitaxel are considered among the most potent chemotherapeutic agents to be used in neoadjuvant or adjuvant treatment, especially in

breast cancer. These fibrotic changes are not always reversible after discontinuation of the drug [170].

Skin Atrophy: 5-FU and hydroxyurea may induce skin atrophy that can persist after discontinuation of the drugs. Collagen, hyaluronic acid, or other fillers can be used to manage such atrophy if it occurs in noticeable areas [171].

Alopecia: Chemotherapy-induced alopecia (CIA) is very frequent during chemotherapy. Severity depends on the chemotherapeutic agent, dosing, method of administration, and time intervals between infusions. Hair loss is seen 1–3 weeks after initiating treatment. Hair will start growing again 2–3 months after completion of chemotherapy. Most patients report changes in color and texture in newly grown hair. Alopecia is related to a significant psychosocial impact, especially in women [172]. Endocrine therapy-induced alopecia (EIA) is less known to clinicians. It usually involves the crown of the scalp and leads to recession of the frontal and bitemporal hairline. Aromatase inhibitors are more likely to induce alopecia, between 6 and 18 months after therapy initiation [173].

The administration of biotin or orthosilicic acid can be considered as an initial treatment. A therapeutic option is the use of topical minoxidil 5% to push hair growth after completion of chemotherapy. Spironolactone has shown some effects in EIA, but the risk-benefit ratio must be considered and its use is not generally recommended. In eyelash hair loss, bimatoprost ophthalmic solution can be considered.

Aids such as hats, scarves, or wigs are often needed and should be routinely prescribed [163].

Chronic Radiation Dermatitis: After radiation therapy, chronic dermatitis develops months to years later. These dermatologic changes include hyper- or hypopigmentation, scaling, xerosis and thickened or hyperkeratotic skin. Additionally, irradiated skin is lacking hair follicles or sebaceous glands and prominent blood vessels (telangiectasias) will develop [162]. Different treatment modalities such as pulsed dye laser for telangiectasia, hyperbaric oxygen therapy to alleviate the pain caused by edema or erythema exist. Keratolytic agents to treat scaling and xerosis can be considered [162, 174].

Secondary skin cancer: Basal cell carcinoma and squamous cell carcinoma of the skin are currently seen in cancer survivors as therapy-related skin cancers. These cancers could be related to factors causing primary cancer, such as smoking, alcohol abuse, changes in hormonal or immunologic status (e.g., immunosuppressive therapy), and environmental factors. Direct carcinogenic effects of cytotoxic agents and radiation therapy must be considered. Dermatologic follow-up of cancer survivors with higher risk of developing secondary skin cancers should be monitored regularly [175]. Importantly, cutaneous metastases can occur as a sign of recurrence, especially when located on the chest or trunk. Sometimes their appearance is unimpressive and may be overlooked. Persistent nodules or firm papules occurring in cancer survivors should be evaluated carefully. In case of suspicious skin changes, a biopsy should be considered [176, 177].

Graft-vs-Host Disease (GvHD): In cancer survivors after stem cell transplant (SCT) chronic GvHD of the skin is defined as occurring 100 days after SCT. It is

usually associated with xerosis and adequate management with alcohol-free skin moisturizers and soft gentle soaps is essential. Other cutaneous manifestations of chronic GvHD include diffuse alopecia and sclerodermoid skin changes. Mucosal changes can lead to oral mucosa atrophy, erosions and ulceration, pyogenic granulomas, xerostomia, oral lichen planus–like changes, and submucosal fibrosis. Glucocorticoids and immunosuppressive therapy are therapeutic options [178, 179].

Nausea and Emesis

Nausea and emesis are symptoms that mostly belong to acute toxicity after systemic cancer treatment or radiation therapy. In cancer survivors, these symptoms are rarely related to a delayed systemic side effect. If nausea and emesis occur with acute onset during survivorship the underlying cause should be elucidated.

Work-up and treatment will not be discussed here.

Respiratory Symptoms

After complete or partial pneumonectomy patients may develop chronic pain, fatigue, shortness of breath, or even respiratory failure on exertion. Radiation or different chemotherapies with or without surgery may initiate or aggravate lung symptoms. Respiratory symptoms can be subdivided from their origins:

- Surgery side effects
- Radiation side effects
- Chemotherapy side effects

Different lung pathologies need to be thought about when seeing patients during or after cancer treatments. It is important to monitor pulmonary function when suspecting symptoms attributable to pulmonary toxicity. There is a prominent part of patients developing abnormal pulmonary function tests after cancer treatment [180] [181].

After childhood cancer, 44–65% develop an abnormal pulmonary function test, which is highest after lung radiotherapy, past bleomycin treatment, or thoracotomy. Restrictive lung diseases as well as decreased carbon monoxide diffusion capacity are the main issues although there is no direct correlation with clinical symptoms. About patients with diagnosed restrictive lung disease, only 9.5% reported dyspnea and 7.5% had noticeable asthma [182].

Among lung cancer survivors treated with pulmonary surgery, dyspnea appears in two-thirds of patients in the long course. Major risk factors are the presence of preoperative dyspnea, reduced diffusing capacity, clinically significant depression symptoms, and lack of physical activity [183]. A myriad of variables influences the presentation of respiratory symptoms among long-term survivors. Mainly aging by

itself, active or stopped tobacco use and cardiovascular comorbidities influence respiratory symptoms and alter pulmonary function. About half of patients stop smoking with diagnosis of lung cancer, but tobacco-related effects due to long-term damage continue.

The degree of lung resection (pneumonectomy vs. lobectomy, sleeve resection, segmental wedge resection) has been associated with varying degrees of pulmonary and functional status compromise [184]. Pneumonectomy leads to a reduction of exercise capacity by one-fourth, whereas the resection of less lung volume as for lobectomy, wedge, and sleeve resections does not affect exercise capacity. Lung volume reduction is here at a maximum of 20% [185].

Pneumonitis

After Radiotherapy, pneumonitis can occur in the early posttreatment phase and include symptoms like dyspnea, nonproductive cough, fever, and hypoxia. The incidence and severity of radiation are correlating with the lung volume irradiated, total irradiation dose, and radiation fractions. It typically occurs after radiotherapy for lymphoma, after whole-body radiotherapy for leukemia or after cancer of the lung, breast, esophageal cancer, or bone metastasis. Radiation pneumonitis can transform into fibrosis [186].

After chemotherapy, or even during, the development of an interstitial pneumonitis can be a severe and fatal complication. Bleomycin is the most common drug inducing pneumonitis and is usually used in the treatment of testicular cancer and Hodgkin lymphoma. Other pneumonitis-inducing drugs are cyclophosphamide, methotrexate, melphalan, carmustine, and immunotherapy agents.

Bleomycin induced pneumonitis (BIP) occurs in up to 46% of patients having received bleomycin and can potentially progress into lung fibrosis which is again associated with a higher mortality. Early-onset pneumonitis occurs while on treatment and can be a life-threatening complication. Late-onset BIP usually develops more than 6 months after the end of treatment. Patients complain of dyspnea associated with a nonproductive cough, fever, tachypnea, and hypoxia [187]. As many as 1% die from pulmonary consequences of bleomycin therapy [188]. The incidence of bleomycin-related pulmonary disease is significantly greater in those who received a total dose of more than 450 mg, with a 10% death rate in those who received a cumulative dose of more than 550 mg. The absolute maximum cumulative bleomycin dose for an individual patient has therefore been suggested to be 300–400 mg maximum.

Risk factors for the development of BIP are beside the dose of bleomycin, age of patient, smoking, renal dysfunction, additional radiotherapy, and the administration of oxygen.

Typical radiographic findings are bilateral bibasilar infiltrates which appear earlier on CT scan than pain radiographic imaging. Small linear and subpleural nodular lesions are typical first CT findings. They can be followed by a diffuse interstitial and alveolar infiltrate. In these cases lobar consolidation ultimately develops.

There are no proven effective treatments for BIP in humans, although corticosteroids are widely applied and should then be used in high dosages (prednisone 1 mg/kg body weight) especially in early-onset BIP. There is no convincing data for late-onset BIP treatment.

Fibrosis

Fibrosis can develop in the course of pneumonitis and typically is a life-threatening complication with a bad prognosis. It potentially occurs among others mainly after bleomycin, busulfan, carmustine, and radiotherapy. Usually fibrosis develops at least 6–24 months after the completion of radiotherapy presenting with progressive dyspnea and cough.

Pulmonary Hypertension

There is a few data showing the possibility of developing pulmonary hypertension after chest radiotherapy or anthracycline chemotherapy. As heart echography shows increased tricuspid regurgitant jet velocity, an association with radiotherapy and pulmonary vascular damaging is discussed. One-fourth of patients having received chest radiotherapy showed increased tricuspid regurgitant jet velocity and appeared limited on a 6-min walk test [189].

Secondary Lung Cancer

Chest radiotherapy increases the risk of developing a secondary lung cancer. In a study of Hodgkin lymphoma survivors, the relative risk was 2.7–7.0 for developing lung cancer when treated with chest radiotherapy [190].

Among breast cancer survivors adjuvant radiotherapy leads to a higher relative risk of 1.49 to develop lung cancer more than 15 years after the end of treatment [191].

Bronchiolitis Obliterans Syndrome and Idiopathic Pneumonia Syndrome

These complications are a special issue after hematopoietic cell transplantation. They are a significant source of morbidity and mortality in these vulnerable patients.

One in ten will develop late noninfectious pulmonary complications more than 3 months after transplantation. Survival of those patients is significantly altered [192].

Bronchiolitis obliterans syndrome (BOS) is a graft-versus-host disease associated complication of allogeneic stem cell transplantation appearing mostly in the first 2 years after transplantation but can appear later. It causes airflow obstruction

secondary to progressive circumferential fibrosis with consecutive scarring of terminal bronchioles [193].

At an initial phase, there are no obvious symptoms except unspecific mild dyspnea on exertion or nonproductive variable cough. Later on patients develop significant dyspnea on exertion and persistent cough. They may then suffer from persistent hypoxia and are oxygen-dependent which aggravates the risk of developing infectious pneumonia. It is then a life-threatening complication with bad long-term outcomes. Steroids are most often used although there are no trials proving their benefit. Five-year survival of patients with BOS was 10% when not responding to steroids, 79% in responders [194].

Therefore, routine lung function testing is recommended at 3, 6, 9, 12, 18, and 24 months after allogenic stem cell transplantation (ASCT) [195].

Idiopathic pneumonia syndrome (IPS) occurs in about 12% of patients after ASCT and was defined as idiopathic syndrome of pneumopathy after ASCT, with evidence of widespread alveolar injury and in which infectious etiologies and cardiac dysfunction, acute renal failure or iatrogenic fluid overload have been excluded. It can appear early in the posttransplantation course and the median onset is about 6–7 weeks [196].

IPS is associated with dyspnea, nonproductive cough, hypoxemia, non-lobar infiltrates, and rapid respiratory failure up to death. Etanercept, an anti-TNF-alpha antibody, is the only treatment that has shown some benefit [197].

Importance of early detection and treatment of respiratory problems needs to be stressed as there is a higher likelihood of dying from a pulmonary cause—8.8 times more as found by Armstrong GT—after chemotherapy and/or radiotherapy of the chest [189].

Cardiac Symptoms

A large number of adult patients who are long-term cancer survivors, present with a myriad of cardiovascular symptoms. Cancer survivors have besides their treatment-related long-term cardiovascular side effects an increased incidence of hypertension, dyslipidemia, diabetes, and obesity aggravating cardiovascular disease like coronary disease, cardiomyopathy, heart failure, valvular disease, and stroke [198, 199].

Common risk factors are more strongly associated with the risk of incident cardiovascular disease in cancer survivors as compared with non-cancer controls [200]. This significantly increases morbidity and mortality in this population.

Hypertension

The incidence of hypertension is higher in cancer survivors than in a comparative population and hypertension may already occur while on treatment. The regular use of corticosteroids in the prophylaxis of nausea, the use of vascular endothelial

growth factor receptor (VEGFR) inhibitors, and multikinase inhibitors increase the rate of hypertension.

At a median duration of follow-up of 11.2 years, the risk of hypertension in testicular cancer survivors was significantly higher and greatest in patients having received more than 850 mg of Cisplatine during their adjuvant treatment [201]. Another study confirms this finding by proving that at 19 years after chemotherapy treatment, patients needed significantly more antihypertensive medication than patients not having had a previous chemotherapy [202].

Arterial hypertension has an additional unfavorable effect on the development of coronary artery disease, heart failure, valvular disease, and arrhythmia. Moreover, the combined effect of chemotherapy and radiotherapy of the chest potentiates the risk of cardiovascular events [3].

Recommended treatment are those that are effective at preventing adverse cardiac remodeling such as angiotensin-converting enzyme inhibitors, beta-blockers, or angiotensin receptor blockers. When using VEGF-inhibitors a vasodilator agent may be beneficial as they have a counter-effect on arterial stiffness, pulsative or resistive load.

Hyperlipidemia

Many drugs used in anticancer treatment, especially in the adjuvant situation, increase lipid levels. This should be taken into account while seeing cancer survivors.

Patients with breast cancer on aromatase inhibitors have a significant increase in hypercholesterolemia as compared to those on tamoxifen [203]. Anastrozole may induce slightly more hypertriglyceridemia and hypercholesterolemia as compared to exemestane [204].

More than half of patients after allogenic stem cell transplantation develop hypercholesterolemia and hypertriglyceridemia. Graft-versus-host disease (GVDH) is as well associated with both [205].

Testicular cancer survivors have a higher incidence of Hyperlipidemia and are more often on lipid-lowering treatments [5].

Androgen deprivation therapy (ADT) in prostate cancer is correlated with an increased risk of developing metabolic syndrome, diabetes mellitus, and cardiovascular disease. ADT induces a change in body composition, decreasing lean body mass and increasing fat mass, and altering insulin sensitivity [206].

Valvular Heart Disease

Over a time of up to 50 years after cancer treatment with anthracyclines or radiotherapy of the chest [207], patients are at higher risk for developing valvular abnormalities, pericardial disease, and heart failure.

Mediastinal radiation is a great risk factor for developing stenosis of valvular regurgitation in a long-time course. 28% of 1800 adult survivors of childhood

cancer had proven valvular regurgitation or stenosis after at least 10 years later [10]. After mediastinal irradiation for Hodgkin Lymphoma, the diagnosis of valvular damage is dose-dependent, and the most common valvular abnormality is aortic stenosis followed by mitral regurgitation, mitral stenosis, tricuspid regurgitation, and aortic regurgitation [208].

Recommendations from the American Society of Clinical Oncology for preventing and managing cardiac dysfunction in adult cancer survivors were set up by an expert panel to give guidance about the screening and follow-up of patients receiving or having had potential cardiotoxic treatments [209].

Pericardial Disease

Pericardial effusion is very rare in the long-term course but can occur during cancer treatment as an acute side effect or complication of the disease. According to the extended and eventual cardiac tamponade, a percutaneous drainage is necessary. Incidence is very low in the long-term course. It manifests as pericardial effusion or pericardial constriction and can best be followed by echography.

Conduction Disease

Structural damage caused by mediastinal radiotherapy can be associated with conduction disease [210]. Symptomatic patients may present sick sinus syndrome, bradycardia, or heart block. If there is no indication for pace-maker they can be followed by ECG and eventual invasive electrophysiological assessment may be necessary according to the specific problem.

Cardiomyopathy

The development of heart failure is an important long-term side effect of cancer treatment which is associated with high mortality and morbidity [211]. It mostly occurs in survivors of non-Hodgkin lymphoma, breast cancer, or lung cancer.

At higher risk for developing cardiac dysfunction are patients that have been treated with high-dose cardiotoxic chemotherapy, radiotherapy including parts of the heart or chest radiotherapy in combination with cardiotoxic chemotherapy. Age over 60 at the time of treatment and having preexisting cardiac risk factors or disease are additional risk factors for cardiac dysfunction [12].

Anthracyclines are the chemotherapy agents that are especially linked to cardiotoxicity. Doxorubicin dose above 250 mg/m^2 is associated with an increased risk of heart failure [212]. Daunorubicin seems to be less cardiotoxic in comparison to doxorubicin. The other main anthracyclines are epirubicin, mitoxantrone, and pegylated liposomal doxorubicin. Frequency of anthracycline-related heart failure is about 5% with a cumulative dose of 400 mg/m^2 doxorubicin and is increasing to

48% at 700 mg/m^2 [213]. Data from Hodgkin lymphoma survivors show that the combination of doxorubicin administration and radiotherapy is associated with higher cardiotoxicity and should no more be applied concomitantly.

Another drug is trastuzumab which is generally well-tolerated with the potential for variable trastuzumab-induced cardiotoxicity as the morbidity of primary concern, ranging from asymptomatic decline in left ventricular ejection fraction (LVEF) to symptomatic heart failure. It is not related to either dose or duration of treatment. The mechanism by which trastuzumab causes cardiotoxicity is not completely understood, but it is thought to be related to blocking of the normal physiologic action of HER2 on cardiomyocytes as well as potential effects on the function of resident cardiac stem cells [214]. Early induced cardiotoxicity is generally reversible and can be treated with beta-blockers and angiotensin-converting enzyme inhibitors. Episodes of trastuzumab-induced cardiotoxicity may have long-lasting effects on cardiac health suggesting that even if left ventricular ejection fraction (LVEF) recovers, the damage may leave the patient susceptible to future insults [215].

For the follow-up of these patients, there are some data showing that cardiac biomarkers such as Troponin I or B-type natriuretic peptide (BNP) may be helpful to early detection of cardiotoxicity. After anthracycline use, most heart failure appears during the first year after completion of therapy. Cardiotoxicity is defined by heart muscle damage leading to a decline of left ventricular ejection fraction (LVEF) which may induce cardiomyopathy.

It is important to detect a decrease of LVEF of more than 10% to less than 50% as early as possible as treatment can lead to substantial improvement in LVEF to even normal levels [216].

For patients undergoing cardiotoxic treatment appropriate regular cardiac check-up is needed to guarantee optimal outcomes. In order to prevent adverse cardiac remodeling the use of angiotensin convertase inhibitors, angiotensin receptor blockers, and beta-blockers are recommended. Additional attention should be drawn to hyperlipidemia, weight control, and regular exercise.

Important recommendations were given through data of the Childhood Cancer Survivor Study cohort in 2015 and should be applied to any patient having had potentially cardiotoxic treatment [217]:

- Childhood cancer survivors treated with anthracyclines or chest radiation are at increased risk of cardiomyopathy.
- Surveillance using echocardiography should be lifelong and performed at a minimum of every 5 years.
- Given the increased cardiometabolic demand on the heart of the mother during pregnancy, closer monitoring of survivors during pregnancy is warranted.
- Survivors with documented asymptomatic cardiomyopathy should be referred to a cardiologist for further diagnostic work-up and possible treatment.
- At-risk cancer survivors should be regularly screened for traditional cardiovascular risk factors (i.e., hypertension, diabetes, dyslipidemia, overweight/obesity) and should be counseled against smoking and physical inactivity.

Harmonized recommendations for cardiomyopathy surveillance for childhood cancer survivors [217]

General recommendation
Survivors treated with anthracyclines and/or chest radiation and their providers should be aware of the risk of cardiomyopathy.

Who needs cardiomyopathy surveillance? Anthracyclines
- Cardiomyopathy surveillance is recommended for survivors treated with high-dose (≥250 mg/m^2) anthracyclines.
- Cardiomyopathy surveillance is reasonable for survivors treated with moderate dose (≥100 to <250 mg/m^2) anthracyclines.
- Cardiomyopathy surveillance may be reasonable for survivors treated with low-dose (<100 mg/m^2) anthracyclines.

Who needs cardiomyopathy surveillance? Chest radiation
- Cardiomyopathy surveillance is recommended for survivors treated with high-dose (≥35 Gy) chest radiation.
- Cardiomyopathy surveillance may be reasonable for survivors treated with moderate dose (≥15 to <35 Gy) chest radiation.
- No recommendation can be formulated for cardiomyopathy surveillance for survivors treated with low-dose (<15 Gy) chest radiation with conventional fractionation.

Who needs cardiomyopathy surveillance? Anthracyclines + Chest radiation
- Cardiomyopathy surveillance is recommended for survivors treated with moderate-high dose anthracyclines (≥100 mg/m^2) and moderate-high dose chest radiation (≥15 Gy).

What surveillance modality should be used?
- Echocardiography is recommended as the primary cardiomyopathy surveillance modality for assessment of left ventricular systolic function in survivors treated with anthracyclines and/or chest radiation.
- Radionuclide angiography or cardiac magnetic resonance imaging (CMR) may be reasonable for cardiomyopathy surveillance in at-risk survivors for whom echocardiography is not technically feasible/optimal.
- Assessment of cardiac blood biomarkers (e.g., natriuretic peptides) in conjunction with imaging studies may be reasonable in instances where symptomatic cardiomyopathy is strongly suspected or in individuals who have borderline cardiac function during primary surveillance.
- Assessment of cardiac blood biomarkers is not recommended as the only strategy for cardiomyopathy surveillance in at-risk survivors.
- Cardiomyopathy surveillance is recommended for High-Risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis, and continued every 5 years thereafter.
- More frequent cardiomyopathy surveillance is reasonable for High-Risk survivors.
- Lifelong cardiomyopathy surveillance may be reasonable for High-Risk survivors.

At what frequency should surveillance be performed for Moderate/Low-Risk survivors?
- Cardiomyopathy surveillance is reasonable for Moderate/Low-Risk survivors to begin no later than 2 years after completion of cardiotoxic therapy, repeated at 5 years after diagnosis, and continue every 5 years thereafter.
- More frequent cardiomyopathy surveillance may be reasonable for Moderate/Low-Risk survivors.
- Lifelong cardiomyopathy surveillance may be reasonable for Moderate/Low-Risk survivors.

At what frequency should surveillance be performed for survivors who are pregnant or planning to become pregnant?
- Cardiomyopathy surveillance is reasonable prior to pregnancy or in the first trimester for all female survivors treated with anthracyclines and/or chest radiation
- No recommendations can be formulated for the frequency of ongoing surveillance in pregnant survivors who have normal LV systolic function immediately prior to or during the first trimester of pregnancy.

What should be done when abnormalities are identified?

- Cardiology consultation is recommended for survivors with asymptomatic cardiomyopathy following treatment with anthracyclines and/or chest radiation.

What advice should be given regarding physical activity and other modifiable cardiovascular risk factors?

- Regular exercise, as recommended by the AHA and ESC, offers potential benefits to survivors treated with anthracyclines and/or chest radiation.
- Regular exercise is recommended for survivors treated with anthracyclines and/or chest radiation who have normal LV systolic function.
- Cardiology consultation is recommended for survivors with asymptomatic cardiomyopathy to define limits and precautions for exercise.
- Cardiology consultation may be reasonable for High-Risk survivors who plan to participate in high-intensity exercise to define limits and precautions for physical activity.
- Screening for modifiable cardiovascular risk factors (hypertension, diabetes, dyslipidemia, obesity) is recommended for all survivors treated with anthracyclines and/or chest radiation so that necessary interventions can be initiated to help avert the risk of symptomatic cardiomyopathy.

Deep Vein Thrombosis and Pulmonary Embolism

Venous thromboembolism (VTE) is a highly prevalent and potentially fatal disease. Cancer has been associated as the most relevant risk factor, before others like hormone use, immobility, or obesity. Annual incidence of VTE in patients with cancer is 0.5% versus 0.1% in patients without cancer.

Data from the Framingham Heart Study demonstrated that in a prospective cohort of 9754 patients, cancer-associated thrombosis (CAT) had worse survival among VTE patients [218]. In the same direction, data from the Global Anticoagulant Registry in the Field (GARFIELD)-VTE registry demonstrated that in a cohort of 10315 VTE patients, from 419 centers and 28 countries, overall mortality was 9.7% in 6 months and 54.3% of all deaths were cancer-related [219]. Concluding that cancer is a major cause of death in VTE patients and vice versa. VTE is the second most prevalent cause of death from cancer, second only to cancer itself [220].

Patients having had a cancer-associated deep vein thrombosis are at risk of developing a postthrombotic syndrome. There is no clear definition but it constitutes of various clinical signs and symptoms such as heaviness, swelling, edema, skin indurations, hyperpigmentation, venous ectasia, redness, and pain during calf compression, cramps, pruritus, and paresthesia. The incidence of postthrombotic syndrome is between 17% and 50% of patients 1 year after VTE. Although most appear during the first 2 years, some take up to 5–10 years to manifest [221].

Once the diagnosis is made, there is a lifelong need toward limiting progression and complications. For this, the only treatment is the use of elastic compression stockings to reduce venous hypertension and improve tissue microcirculation. In severe cases, the use of topical dressing and intermittent pump compression is needed. The risk for another deep vein thrombosis is higher.

A single randomized trial showed that the use of elastic stockings for at least 2 years after proximal DVT reduced the rate of postthrombotic syndrome by 50% [222].

Around 2–4% of patients with pulmonary embolism will have chronic damage to the lungs known as pulmonary hypertension which is characterized by shortness of breath, tiredness, sometimes chest pain, and decreased exercise ability. Pulmonary hypertension can lead to heart failure if untreated. Pulmonary hypertension must be taken into account after large pulmonary embolism especially during the months after the acute event if the concerned patient does not get back to the previous condition. Some complaint of shortness of breath and chronic fatigue long after the pulmonary embolism has been treated and resolved. After pulmonary embolism, 47% of patients show a significant reduction in their physical well-being more than 1 year after the thromboembolic event [223].

Long-term consequences of pulmonary embolism often go far beyond the physical ones. Patients experience symptomatic embolism as a distressing severe event with existential fears which may lead to behavioral changes, depression, or to a post-traumatic stress disorder (PTSD). Regular psychological interventions or even drug treatment may be necessary [224].

As referred to previously, the occurrence of deep vein thrombosis and/or pulmonary embolism after cancer can be the first sign of cancer recurrence.

Endocrine Disorders

Best available data about the broad range of endocrine disorders in cancer survivors exists for late effects of childhood cancers. There is an important number of treatment-related factors having an impact on several endocrine functions [225]. They affect problems with thyroid, gonadal and adrenal function as well as growth, weight, puberty, and bone health [226].

Hypothyroidism

Hypothyroidism leads to metabolic changes such as dyslipidemia, hyperglycaemia, and cardiovascular risk increase through altering coagulopathy and endothelial function. It is associated with a higher incidence of diabetes mellitus, cardiovascular diseases, lung diseases, and psychiatric morbidity as well as impaired quality of life.

Especially local radiotherapy to the neck, mediastinum, or the thyroid gland itself induces secondary hypothyroidism. This results in vascular damage in the epithelium of small vessels and transformation of fibrosis of capsular structures. Late irreversible changes consist of atrophy, chronic lymphocytic inflammation, vascular fibrosis, and focal and irregular follicular hyperplasia [227].

Most patients who develop radiation-induced hypothyroidism do so within the first 2–3 years after radiotherapy. A radiation dose-depending probability of the development of hypothyroidism is well known. The addition of chemotherapy to

radiotherapy as in head and neck cancer treatment does not increase the risk. Smaller thyroid glands, as in women compared to men, are at higher risk for developing hypothyroidism [228].

Hypogonadism

The development of hypogonadism and its side effects needs to be thought about after the use of alkylating agents, irradiation of the cranium, pelvic, or gonadal irradiation. The consequences of such treatments concern mainly males, treatment during puberty, or in the post-pubertal period in females.

The etiology of hypogonadism in male is either primary (testicular, hypergonadotropic, or with elevated LH and FSH) or secondary (central, hypogonadotropic, or with low or inadequately normal LH or FSH). Primary hypogonadism in cancer patients can result from inflammatory cytokines and chemotherapeutic agents. Secondary hypogonadism can result from opioid use, glucocorticoid treatments, low leptin levels, or high ghrelin concentrations [229].

Cancer is a proinflammatory state with elevated levels of proinflammatory cytokines which have a direct effect on the hypothalamus-pituitary-gonadal axis and decreasing significantly testosterone levels [230].

High-dose chemotherapies, mainly alkylating agents, are having a direct dose-related toxic effect on Leydig cells function in the gonads leading to a permanent induction of hypogonadism in those patients [231]. Its incidence is proportional to the alkylating drug doses given.

In cancer patients or survivors still suffering from disease- or treatment-related cachexia, low leptin levels lower sex hormone concentration as leptin is secreted by adipocytes. Leptin is responsible for regulating energy homeostasis at the level of the hypothalamus and it is required for normal LH and FSH secretion centrally and production of testosterone in the gonads [232, 233]. Ghrelin is a hormone correlating inversely with leptin levels and its concentration increases with weight loss. High ghrelin levels lead to reduced LH and testosterone concentration [234].

Ongoing opioid use in cancer survivors is associated with a high risk of hypogonadism as opioids can reduce testosterone levels by disrupting the normal pulsatility of gonadotrophin-releasing hormone (GnRH) secretion [235].

Decreased Bone Density

The important use of corticosteroids as a therapeutic agent or in association for antiemetic treatment on a regular basis for more than 2 months (starting at 5 mg prednisone per day or other equivalent corticoids) can induce secondary osteopenia and osteoporosis whereas the risk of osteopenia-related fractures in later life is not proven [236]. Hypothyroidism and/or hypogonadism are influencing bone health by impacting growth hormone stimulation and favor osteopenia on a long term. The

same is true for women with premature menopause after ovariectomy or who are taking antihormonal adjuvant treatments [237], for men under antiandrogenic treatment or secondary hypogonadism after testicular cancer. Other factors increasing the risk of bone-density loss: gastrectomy, several types of chemotherapy (platinum, ifosfamide, doxorubicin, and methotrexate), age over 50, alcohol abuse, and few physical activities.

Preventive measures are oral calcium and vitamin D supplementation, regular physical exercising, limiting caffeine and alcohol intake as well as smoking cessation. Regular bone density scans are recommended and eventual antiresorptive treatment might be indicated [238].

Cancer treatments in early life can as well result in short stature. The risk is higher with early life radiotherapy of the cerebral cortex or in unfractionated (dose of more than 10 Gy) total body radiotherapy. The risk of avascular bone necrosis increases with earlier use of corticosteroids and earlier bone radiotherapy [239].

Obesity and Metabolic Syndrome

Younger treatment age, females, and cranial irradiation of more than 20Gy are risk factors for developing obesity throughout life mainly through the influence of growth hormone deficiency. Metabolic syndrome is the combination of insulin resistance, overweight/obesity, hypertension, and dyslipidemia which is an issue mainly in patients treated with cardiotoxic systemic treatments of radiotherapy [240].

Fertility Disorders and Sexual Dysfunction

Fertility Preservation

Exposure to chemotherapeutic regimens and/or radiation in childhood and adolescent cancer patients severely affects the reproductive ability in the long-term as they are gonadotoxic and induce depletion of the unique follicular pool, leading to premature ovarian insufficiency [241]. About half of male cancer survivors of these age groups experience difficulties to conceive a child during adulthood which presents a significant quality of life and a medical challenge. The most frequent cancers in young boys and adolescents are leukemia, brain and other tumors of the central nervous system, and lymphomas. Testicular cancers are frequently seen in adolescents and young adults. Fortunately, modern treatment leads to a more than 80% 5-year survival rate for childhood cancer [242].

Those treatments often affect fertility as gonadotoxic treatment is mostly substantial and improvement needs to be done. Patients with advanced Hodgkin lymphoma being treated with BEACOPP regimen [243] or anthracycline- and taxane-based treatment in breast cancer [244] have a moderate to high risk of primary ovarian insufficiency.

A variety of fertility preserving and preventing measures can be offered. These multidisciplinary strategies are regrouped under the term Oncofertility [245]. Preventive approaches aiming at the protection of germ cells and testicular function during exposure are preferable. Alternatively, cryopreserved oocyte or immature ovarian tissue can be acquired in women and sperm cryoconservation or testicular tissue collection can be saved before treatment of young men and be later on used for in vitro procreation. For female adolescents and adults of child-bearing age, a pharmacological protection with GnRH analogs can be offered.

The possibility of conceiving with their own gametes and building a family after being cured represents although a top priority for young cancer patients at diagnosis [246].

Sexual Dysfunction

Cancers that do not affect the sexual organs can also affect sexuality by changing the subjective body image. Patients feel less attractive, treatments and the diagnosis itself causes fatigue or depression and decreases interest in sex. Chemotherapy agents are associated in the short and long term with symptoms of the skin including mucosal tissue. This may lead to vaginal dryness, painful intercourse, reduced sexual desire, and the disability to achieve orgasm. Many of these issues are additionally caused by the sudden onset of menopause as a result of cancer treatment [247]. Personal issues related to sexual health can be emotionally draining and can interfere with relationships even though patients would need those most.

Sexual dysfunction in women concerns mainly patients who had pelvic or breast surgery, those with chemotherapy-induced premature ovarian failure or patients on adjuvant endocrine therapy [248]. Aromatase inhibitors induce a low estrogen status and are associated with lower libido, insufficient lubrication, and vaginal atrophy in comparison to tamoxifen [249]. Sexual dysfunction in women is additionally affected by fatigue, reactive depression and anxiety, distress, and changes in body image following surgery of the breasts or pelvic organs.

First-line treatment of sexual dysfunction symptoms in women consists of non-hormonal local treatments like lubricants and moisturizers. If treatment needs to be intensified one may consider the use of local low-dose vaginal estrogens or vaginal dehydroepiandrosterone (DHEA, prasterone). In case of dyspareunia, a local treatment with a lidocaine formula applied to the introitus may be helpful.

Sexual side effects in men are most common after treatment for cancers of the pelvis: bladder, colon, prostate, and anorectal cancer. They very likely cause or accelerate erectile dysfunction which is the most frequent sexual dysfunction in men. Cancer treatments may add a negative evolution to eventual existing sexual dysfunction in older men. Despite the prevalence of erectile dysfunction in male cancer survivors, most are often reluctant to seek treatment. Other symptoms than erectile dysfunction include difficulty climaxing, weaker or dry orgasm, loss of interest in sex, pain during sex, less energy for sexual activity, and feeling less attractive of feeling ashamed because of an intestinal or urinal stoma needing to

wear an ostomy bag. Treatment-induced fatigue, anxiety, depression, and emotional changes can as well cause sexual difficulties and loss of libido.

Open communication with the patient and with their partner helps them address any sexuality issues and the patient may also be referred to a therapist experienced in working with cancer survivors. Sexual validated health questionnaires may be used to evaluate sexual dysfunction and focus on the main issues. The International Index of Erectile Function (IIEF) is a 15-item self-report measure that records erectile function, orgasm, desire, intercourse satisfaction, and overall satisfaction [250].

Therapeutic success often needs a multidisciplinary approach consisting first of medical and psychological support to the patient and maybe the partner. Phosphodiesterase-5 (PDE-5) inhibitors have shown to be effective for erectile dysfunction after surgery or radiotherapy for prostate cancer and may be a useful treatment for erectile dysfunction in cancer patients in general. There is no data that the available agents sildenafil, tadalafil, and vardenafil differ in efficacy, safety, or tolerability [251]. Alternatively, the use of locally applied intraurethral suppositories containing the prostaglandin E1 (PGE-1) analog alprostadil may be used. Intracavernosal injections (ICI) using a single drug alprostadil or papaverine or a combination of phentolamine papaverine and prostaglandin E1 (PGE1) have shown efficacy in patients with no effect on PGE-5 inhibitors [252]. Vacuum devices are an option for men who cannot tolerate or are resistant to systemic PGE-5 inhibitors or local drug treatment. Supplementation of testosterone in male cancer survivors, especially after prostate cancer, should be avoided. For men with other cancers, supplementation should be made on a very individual basis.

Gastrointestinal Disorders

Gastrointestinal symptoms are the most common of all chronic physical long-term side effects of cancer treatment and have a great impact on daily activity.

This is especially true for cancers of the pelvis like cervical, uterine, rectal, or anal cancer. Intestinal cancer needs to be treated with partial resection of bowel resulting in eventual short-bowel syndrome. In those who have undergone local radiotherapy, about 80% develop chronic bowel symptoms and most are affected in their daily life [253].

Gastrointestinal complications were reported in more than 40% of childhood cancer survivors by 20 years after cancer treatment [254]. Radiotherapy induces long-term changes in bowel function and can aggravate over time. There is irreversible induction of fibrosis via progressive endothelial dysfunction and ischemia. Physiological function of the gastrointestinal system is disturbed by most cancer treatments, new gastrointestinal disorders may come up in cancer survivors and other indirectly related factors play a frequent role: preexisting gastrointestinal disease, the psychosomatic effect, and anxieties around the diagnosis of cancer [255].

To aid adequate medical management it is important to follow a few concepts:

- accurately identify troublesome symptoms

- patients usually have multiple symptoms
- symptoms are often multicausal
- simple investigations can identify the causes
- simple treatment approaches ameliorate or resolve the underlying causes [255]

Abdominal and pelvic surgeries often result in partial intestinal resection or induction of postsurgical adhesions. A higher rate of liver conditions like veno-occlusive disease or graft-versus-host disease is seen in patients after bone marrow transplantation with total body irradiation.

Upper Gastrointestinal Tract

Long-term consequences of esophageal cancer might be associated with motility problems of the upper gastrointestinal tract. This begins with trouble swallowing which can lead to nausea, loss of appetite, and weight loss due to reduced caloric intake. Eating habits need to be adapted in frequency and consistency of foods. Some patients, mainly after chemo-/radiotherapy develop esophageal stricture which needs intervention like stent placement or dilatation.

The digestive function of the stomach can be altered after esophagectomy, full or partial gastrectomy leading to a reduced or no capacity of the stomach to hold food for digestion. This can lead to a dumping syndrome in about 20% of patients after gastrectomy and is defined by postprandial diarrhea, abdominal cramps, feeling bloated, sweating, and flushing [256].

An important number of symptoms of the upper gastrointestinal tract have been identified and can be managed by gastroenterologists, specialized nurses, and dieticians: heartburn, acid or bile reflux, burping/belching, dysphagia, dry mouth, early satiety, oral flatulence, halitosis, odynophagia, jaundice, gastric stasis, pain, regurgitation, vomiting, weight loss, and hypersalivation [257].

Partial or complete gastrectomy changes digestion and alters absorption of nutrients like vitamin B12, folates, or calcium. Special care needs to be taken to prevent deficiencies that result in postgastrectomy syndrome which includes anemia as a result of vitamin B12 or iron malabsorption and osteoporosis.

Following partial gastrectomy, the remnant stomach is susceptible to developing ulcer disease or cancer.

In postgastrectomy patients, retained gastric antrum and incomplete vagotomy are the two main surgical causes of recurrent peptic ulcer disease but they can be due to Helicobacter pylori infection, Zollinger-Ellison syndrome, gastric remnant cancer or medicines side effects like use of nonsteroidal anti-inflammatory drugs.

Chronic reflux of bile and pancreatic enzymes cause chronic inflammation and favorably influence the development of gastric remnant cancer. The risk of remnant cancer increases with time after initial surgical treatment. Endoscopic surveillance can be offered and is urgent in upcoming new symptoms.

Lower Gastrointestinal Tract

Best known long-term complications of gastrointestinal cancers are those associated with treatments of pelvic cancer.

There is a multitude of symptoms, occurring alone or simultaneously, being reported after pelvic radiotherapy: bloating, abdominal or anorectal pain, nausea, constipation, evacuation difficulties, tenesmus and bleeding, diarrhea and steatorrhoea, changes of bowel habits, irregular defecation, evacuation difficulty and variable incontinence [258].

Chronic diarrhea is a long-term complication in about half of survivors after the treatment of colorectal carcinoma and it has a profound impact on quality of life [259]. Often the problem is not spontaneoulsy stated by the patient who has accepted it as an inevitable consequence. Patients need to be asked about potential symptoms of radiation proctitis which appears mostly at least 1 year after the end of pelvic radiotherapy. The fibrotic transformation of anorectal mucosa induces new upcoming symptoms like diarrhea, rectal urgency, pain, obstruction, and bleeding. Symptoms can be similar in secondary bowel obstruction. The incidence of intestinal fibrosis is dose-dependent, 5% at 40 Gy and up to 40% at 60 Gy [260]. The risk is higher after the combination of abdominal radiation and surgery but can happen after partial colon resection for colon cancer.

Survivors are at risk for bowel obstruction, either as a result of strictures, following radiotherapy-induced fibrosis or due to altered motility after chemotherapy with a vinca-alkaloid.

Anorectal function declines the lower the surgical anastomoses are and whether they additionally received chemo-/radiotherapy or radiotherapy [261]. Patients complain of increased stool frequency, incontinence and perianal irritation, decreased stool and flatus discrimination, more incomplete evacuations, and decreased rectal compliance [262].

Management of diarrhea consists of antidiarrheal medications as needed and dietary adjustments. Reduction of raw vegetables, low-fat diets, probiotic complementation, and elemental diets may be beneficial. Pain, intermittent diarrhea in anastomosis stenosis, or radiation-induced strictures can be relieved by stool softeners.

Treatment of stool incontinence is multifactorial: avoidance of foods like incompletely digested sugars or caffeine, avoidance of activities that worsen symptoms, optimize perianal skin hygiene and eventual application of a barrier cream like zinc oxide, biofeedback therapy to improve control of the pelvic floor and abdominal wall musculature, and rarely surgery.

Follow-up endoscopic exams are important as the risk of developing a second colorectal cancer either after pelvic radiotherapy or after a first colorectal cancer is higher than in the general population [263]. The possibility of a genetic form of colorectal cancer needs to be kept in mind as those patients may need more frequent endoscopic exams. In patients with Lynch syndrome colonoscopy might be more often as tumors may develop quite rapidly.

Urologic Disorders

Bladder function of collection and excretion of urines may be altered following intravesical, locoregional, surgical, or systemic cancer treatments. Bladder dysfunction is a common concern in patients after treatment of different pelvic cancers like cervical, uterine, rectal, or anal cancer. Quality of life is impaired in up to 50% of patients over a 20-year period after radiotherapy of the pelvis. Particularly those having been treated with chemo-/radiotherapy for rectal cancer or cervical cancer seem to be concerned with urinary dysfunction in over 20% [264]. Typical symptoms of bladder dysfunction are urinary frequency, urgency, dysuria, and hematuria. Signs of radiogenic toxicity include detrusor instability, bladder ulceration, and vesicovaginal fistula [265]. In the short-course postoperative phase symptoms like urinary incontinence, urgency or urinary tract infections are mostly reversible until 2 years after treatment.

Hemorrhagic Cystitis

Hemorrhagic cystitis in the short-course after treatment with ifosfamide or cyclophosphamide chemotherapy is a sterile cystitis with macroscopic hematuria. It is less common as a late toxicity of pelvic radiation therapy when the bladder is within the radiation treatment field. Ifosfamide and cyclophosphamide are approved for use in a variety of malignancies, both in children and adults. Cyclophosphamide is also used as a component of conditioning regimens prior to hematopoietic cell transplantation.

Hemorrhagic cystitis is a complex inflammatory response that is induced by a toxic metabolite (acrolein), with subsequent activation of immunocompetent cells and release of many proinflammatory agents [266]. Accumulation of acrolein in the bladder causes local cell death and activation of proinflammatory cytokines in the urothelium which results in the cessation of protein production and damage to the integrity of the bladder urothelium with swelling, bleeding, and ulceration of the bladder mucosa.

Radiation Cystitis

Radiation cystitis is a late complication of pelvic radiation therapy that can occur months up to 20 years after administration. It occurs in 6.5–9% of patients after radiotherapy of the prostate for gynecologic cancer and is severe in less than 5% [267]. Involved bladder tissue becomes edematous and friable which later on turns into ischemia and fibrosis of the mucosa and submucosa. Dilated and fragile teleangiectatic vessels develop and are prone to bleed. Its development is dependant on the total radiation dose administered, the dose per fraction, and the volume of the bladder being in the radiation field. Focal radiation involvement with higher doses

can result in local ulceration and bleeding [268]. Highest risk is in patients with radiation of more than 75 Gy of the bladder neck. Besides dose and volume, antiandrogenic treatment and previous prostate transurethral resection are risk factors for hemorrhagic cystitis.

Management of hemorrhagic cystitis is mainly based on the severity of hemorrhagic cystitis. There are no evidence-based guidelines. Most cases are mild and can be managed by balanced hydration. In case of emergency presentation, standard measures include sufficient hydration, bladder washouts, clot evacuation, continuous bladder irrigation, and supportive treatment for pain and blood loss. Further on medical or surgical treatments are associated with higher difficulty and mortality [269]. Urinary diversion by nephrostomy and emergency cystectomy for end-stage hemorrhagic cystitis is associated with a 44% mortality rate [270]. Alternative less invasive management options for non-emergent hemorrhagic cystitis include systemic medical therapies (alkylating agents, formaline or album), hyperbaric oxygen, intravesical therapies, and laser ablation.

Bladder Fibrosis

Long-term bladder fibrosis and contracture have been reported in patients previously treated for hemorrhagic cystitis. It is a fibrotic irreversible transformation of the bladder urothelium and leads to functional impairment. Few data exist on childhood cancer survivors. In 23 patients with previous hemorrhagic cystitis after childhood cancer treatment with cyclophosphamide, three developed bladder contracture. Eighteen of those had also undergone radiation treatment [271]. These late changes are attributed to irreversible fibrosis as a consequence of collagen deposition in the bladder wall. Cumulative radiation dose >45 Gy to the whole bladder poses the highest risk for bladder toxicity [272]. Patients present abnormal bladder capacity and difficulty voiding normally. Urodynamic studies show a reduced bladder function.

Neurogenic Bladder

Systemic or local cancer treatment can potentially injure bladder innervation and can have negative effects on bladder storage, on voiding or continence. Injury can happen on several levels from brain to peripheral nerves by tumor growth, surgery, radiotherapy, or chemotherapy.

Causes in the central nervous system lead to bladder incontinence whereas spinal cord injury results in detrusor overactivity and poor storage whereas initially there may be impairment of bladder emptying. In the longer term, there is disturbed coordination between the bladder and external sphincter.

Impaired bladder contractility results from either pelvic surgery or radiotherapy to the lumbar or sacral spine [273].

Secondary Malignancy of the Bladder

Previous cancer treatment especially with cyclophosphamide may be associated with a higher risk of secondary bladder cancer which is most commonly symptomatic via macrohematuria. Most of these carcinomas are in a local stage, low grade, and associated with a favorable prognosis after local treatment. Cyclophosphamide has been associated with new bladder cancer [274] and leiomyosarcoma [275] of the bladder but still seems to be rare. A report from the Childhood Cancer Survivor Study found only five cases of secondary bladder cancer among 13,136 patients [276].

Ophthalmological Disorders

Neurosensory complications affecting the auditory, ocular, olfactory, or speech systems are commonly reported by survivors. A prospective study found that 22% of childhood cancer survivors reported auditory or ocular late effects during the first decade following treatment [277]. Ocular sequelae observed in childhood cancer survivors include cataracts, keratoconjunctivitis sicca, and vision loss. Treatment-related factors, specifically radiation and glucocorticoids, are established risk factors for the development of eye-related complications [278].

Late ocular conditions by their relative risk compared to siblings at least 5 years after treatment in childhood cancer survivors according to the Childhood Cancer Survivor Study [279]:

- Cataracts—relative risk 10.8 (6.2–18.9)
- Double vision—relative risk 4.1 (2.7–6.1)
- Legally blind—relative risk 2.6 (1.7–4.0)
- Dry eyes—relative risk 1.9 (1.6–2.4)
- Glaucoma—relative risk 1.5 (1.1–5.7)
- Retinal conditions—relative risk 1.3 (0.9–2.0)

Cataract

The lens is the most sensitive structure of the eye to the effects of ionizing radiation. Early studies in adults found that a single dose of 200 cGy or multiple, fractionated doses of radiation at a minimum total dose of 400 cGy could lead to cataract formation [280]. Steroid treatment for graft-versus-host disease is an additional factor for cataract development in patients after total body irradiation for hematological cancers [281] but the general use of corticosteroids and risk for cataract is not well-proven. In the CCSS-cohort prednisone was associated with cataract formation, while dexamethasone use was not. The greatest risk of cataracts is in patients after leukemia and primary CNS malignancy treatment [279].

Legal Blindness or Visual Function Deficit

Legal blindness is mostly defined as the inability to see at least 20/200 in either eye with the best possible optical correction. It is defined to either limit activities or to provide benefits to those who need assistance with daily activities. It can be due to multiple eye conditions like diabetic retinopathy, macular degeneration, rheumatic injuries, or glaucoma.

Radiation doses greater than 500 cGy to the eye are associated with an increased risk of legal blindness in that eye at a median of 1.0 years but the incidence increases up to 20 years post-diagnosis. Cerebral radiation to the posterior fossa with radiation doses >3000 cGy to the temporal lobe are associated with a statistically significant increased risk of reporting being legally blind in one or both eyes. Legal blindness at 20 years is more common in soft tissue sarcoma survivors and in patients with primary CNS malignancy [279].

Keratoconjunctivitis Sicca

A known complication of radiation to the orbit is severe dry eyes, with symptoms increasing when the dose to the eye is >500 cGy [282]. Radiation may damage the lacrimal apparatus through various mechanisms, including scarring of the canaliculi and failure of the lacrimal pump due to decreased eyelid mobility [2].

Diplopia

Double vision may be secondary to ocular and brain conditions. There is a modest correlation between diplopia and other reported ocular conditions like cataracts [279].

Late-onset blindness is reported in a very small percentage of survivors with cataracts and is as well reported in patients with recurrence of malignancy of the central nervous system or who developed a second malignant CNS tumor.

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Management of Cancer-Related Fatigue

11

Florian Strasser

Management of Cancer-Related Fatigue

Fatigue is one very frequent of, if not *the* leading, symptom humans confronted with cancer experience. It can be caused by cancer disease itself, by side-effects of anti-cancer treatments, and by a myriad of somatic, inflammatory, psychological, and cognitive comorbidities. One important feature of fatigue is, that patients dealing with the disability of fatigue often become "fatigued of being fatigued" and develop secondary fatigue-burnout or depressive symptoms. To contribute to excellent care of cancer survivors (people with cancer experience who (a) are cured after cancer therapy, (b) are undergoing adjuvant anticancer treatment in curative intent, or (c) live with advanced, incurable, but well-controlled cancer), it is important as a health care professional to (1) be aware of the silent burden people with fatigue experience, (2) proactively screen these people to give fatigue and its consequences "a voice or a number," (3) identify systematically reversible and nonreversible causes and cofactors contributing to fatigue, (4) categorize people affected by fatigue for those requiring (a) some self-management advice, (b) outpatient fatigue-tailored interventions, or (c) intensive multimodal fatigue management programs, (5) initiate and coordinate these interventions, (6) monitor outcomes and relapses in fatigue-associated burden, and (7) contribute to research related to fatigue in cancer.

History and Literature

Historically the term fatigue in the title of a paper in combination with cancer in the title was first mentioned in Pubmed 1987, interestingly in the first years the articles were mainly in journals from nursing societies. Until today, March 2021, 2130

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papers are mentioned, including 153 reviews (cancer[title] AND fatigue[title] AND review[title]).

The first papers mentioning a guideline were 1998 [1]/1999 [2] followed by the NCCN guideline 2000 [3]. The first ESMO guideline on CRF was published in 2020 [4].

Definition, Classification, and Risk factors

Cancer-related fatigue (CRF) is an experience of a subjective, persistent, feeling of tiredness, weakness, or lack of energy, which is not proportional to recent physical activity (as normal human experience) and is not alleviated through sleep or rest (as normal human experience). Cancer survivors suffering from CRF are therefore very often confronted with lack-of-understanding from non-cancer experienced people, which contributes to distress and also financial and vocational injustices. Phenomenologically CRF is characterized by physical (muscular), emotional, and cognitive components of fatigue, in individually variable degree and combination. CRF can have a major impact on patients' functioning and Quality-of-Life. The first descriptive definition was published in 2000 [1–3] and is still in use.

The following symptoms have been present every day or nearly every day during the same 2-week period in the past month:

Significant fatigue, diminished energy, or increased need to rest, disproportionate to any recent change in activity level

Plus five (or more) of the following:

- Complaints of generalized weakness or limb heaviness
- Diminished concentration or attention
- Decreased motivation or interest in engaging in usual activities
- Insomnia or hypersomnia
- Experience of sleep as unrefreshing or nonrestorative
- Perceived need to struggle to overcome inactivity
- Marked emotional reactivity (e.g., sadness, frustration, or irritability) to feeling fatigued
- Difficulty completing daily tasks attributed to feeling fatigued
- Perceived problems with short-term memory
- Post-exertional malaise lasting several hours

The symptoms cause clinically significant **distress** or **impairment** in social, occupational, or other important areas of functioning.

There is evidence from the history, physical examination, or laboratory findings that the symptoms are a **consequence** of **cancer or cancer-related therapy**.

The symptoms are **not** primarily a consequence of comorbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder, or delirium.

Table from Portenoy RK, Itri LM. Oncologist 1999;4:1–10

There is however no common definition for CRF, between 19 and 24 definitions of CRF utilized to measure CRF are reported [5, 6]. There are also differences in the definition regarding the impact of CRF on functioning [3, 7].

Classification: Cancer vs. Cancertherapy vs. Comorbidity

The term "cancer-related fatigue" (CRF) encompasses fatigue (a) caused by the cancer disease itself and (b) by anticancer treatments. Due to this very broad definition both a post-curative survivor years after being cured from cancer disease and living without active cancer and without anticancer treatment [8] and a patient with active, incurable cancer in a terminal stage days before death experience CRF [9, 10]. It is obvious, that these two situations of CRF, representing the whole spectrum of CRF, are quite different and require more tailored assessment and management. Unfortunately, the term CRF is often used for various situations and even some guideline authors may not differentiate the various CRF-subtypes, with the risk to formulate inappropriate, mostly then false negative, recommendations. In modern oncology sophisticated personalized, biomarker and genetic-testing based, interventions are rapidly developed, accepted, and pursued by the oncology community. Drugs working just for one mutation will not be given to a patient not having the mutation. In CRF, unfortunately, often CRF-patients are not appropriately classified to judge the effectiveness of an intervention in a specific population. It seems indispensable and vital to subclassify CRF into specific subtypes.

Cancer-Disease Related Fatigue: (Pre-) cachexia

Cancer cachexia and cancer-disease related fatigue can be interpreted as similar concepts [11]. The key feature of pre-cachexia is anorexia and fatigue [12] before weight loss occurs. Patients with cancer cachexia experience fatigue, most pronounced in the terminal stage. Typical for the mechanism of cachexia is inflammation, which is also understood as causing factor for fatigue [13]. The very frequent co-occurrence of fatigue and cachexia in patients with advanced cancer is conceptualized as a symptom cluster [14].

Cancer-Treatment Related Fatigue

Anticancer treatment, surgery, radiotherapy, systemic anticancer treatment can cause cancer-treatment related fatigue (CtrF).

- In surgery, a **postoperative fatigue syndrome** is described, but not well understood [15, 16], as also toe broad spectrum of not well understood interventions showcases [17]. It might be associated with symptoms, such as stress, anxiety, depression, pain, or changes in sleep patterns, maybe to anesthesia-related toxicity, but also to the muscle loss after bed rest (1.4 kg muscle per week [18]) and possibly malnutrition.
- Radiotherapy is associated with fatigue, by many clinicians seen as the leading side-effect stimulating clinical trials of toxicity-reducing radiotherapy techniques with the primary endpoint fatigue [19]. As causes for **radiotherapy-induced fatigue** mitochondrial dysfunction, inflammation, neuromuscular or endocrine factors are hypothesized [20], in addition, of course, of possible occurring toxicities such as anemia or malnutrition.
- **Systemic anticancer treatment associated fatigue** encompass chemotherapy (e.g., cell poisons), targeted agents, endocrine agents, and immunotherapy. The

mechanism associated with fatigue encompasses direct muscle toxicity possibly mediated by mitochondria depletion, endocrine alterations, immune alterations and other, only partially understood mechanisms including neuro-immunological, neuromuscular, autonomic dysfunction, complex endocrine mechanism, or others. Taxanes and platins are examples for muscle toxicity impacting mitochondria and disturbing myogenesis [21]. The leading side-effect of checkpoint inhibitors is fatigue [22], but compared to chemotherapy at a lower level [23]. The number of available targeted agents is rapidly increasing, for many of them fatigue is the leading toxicity [24, 25].

Comorbidities-Related Fatigue

Many comorbidities and complications are associated with fatigue. In the 2000 NCCN guideline [3] the authors cite (quote) *"five primary factors are known to be associated with fatigue: pain, emotional distress, sleep disturbance, anemia, and hypothyroidism.*" The list includes many other causes including organ dysfunction (kidney, heart, lung, etc.), electrolyte alterations (hypercalcemia, hypophosphatemia, etc.), endocrine disturbances (hypogonadism, hypocortisolism, etc.), or dehydration.

Classification: Phenomenological

Patients with advanced cancer present a CRF with substantial loss of muscle mass (sarcopenia) and muscle function, compatible with cancer cachexia. Cognitive fatigue is also present, but often less obvious than muscular weakness. In contrast, the CRF of cancer survivors without anticancer treatment and without known active cancer is an "invisible disability" with reduced availability of energy reserves, but with almost normal physical, cognitive and emotional performance for the time span the energy reserves are fully loaded. This time span however can be short up to minimal 15 min or longer up to 4–8 h.

Prevalence of CRF and Risk Factors: Three Important, Exemplary Recent Papers

According to a recent systematic review and meta-analysis involving 71,568 subjects drawn from 129 studies reporting pooled prevalence estimates for fatigue among patients with cancer the aggregate prevalence of fatigue in patients with cancer was 49%, ranging from 11 to 99% [26]. As possible explanation for this variation of the prevalence between the studies the authors hypothesize (quote): "*This could be attributed to the diversity of the assessment scales (cutoff of scales) or unique features of certain types of cancer and cancer treatment strategies that increase the probability of experiencing fatigue. In addition, there is no universally agreed on definition of CRF or gold standard questionnaire to measure this troubling symptom.*"

- As possible risk factors **female gender** was mentioned in 12 studies, then described as an explanation for this observation (Quote): "*This may be because, first, men report fatigue less than women, and second, women are less likely to receive social support*."
- Interestingly an association between mean **age** and overall fatigue prevalence rate could not be shown.
- With regards to the relationship of CRF prevalence and **anticancer treatment** the authors report (quote): "*fatigue prevalence was 62% during anticancer treatment; 50.1% less than three months after curative treatment completed; 43% among those with more than three months after curative treatment completed; and 50.8% in mixed cancer studies.*" This result supports the observation that anticancer treatment can cause CRF supported by mechanistic explanations. The authors further specify (quote): "*The percentage of fatigue during anticancer treatments was expected, as fatigue typically increases during radiation therapy, chemotherapy, and biological therapy*." and (Quote) *"In addition, treatment introduces various toxicities to patients, which will likely increase the experience of fatigue*."
- The data support the observation that **active cancer disease** is a contributor to fatigue. The authors report that (quote) "*studies involving patients with advanced cancer were highest in reporting fatigue with 60.6%, followed by studies that included mixed stages of cancer at 51.5%.*"
- The prevalence of fatigue is different according to **cancer type subgroups**. The authors report (quote) "*Patients diagnosed with gastrointestinal (50%), breast (49.7%), and lymphoma (43.3%) cancers reported highest fatigue compared with patients with gynecological (26.2%) and prostate (26.3%).*"

Over the last decades, the prevalence of CRF decreased from 65.3% in 1996 to 44.4% in 2020. The authors hypothesize that (quote) "*This decrease may be due to the fact that several clinical guidelines were published on the assessment and management of CRF.*" However, another explanation may be that (a) the toxicity of anticancer treatments decreased, immunotherapy is associated with less fatigue than chemotherapy and (b) that supportive and palliative management of cancer patients improved [27].

The **prevalence of fatigue** was explored in a prospective study (FiX study) of 2244 cancer patients approx. Two years after diagnosis using the EORTC QLQ-FA12 questionnaire [28]. Fifty-nine percent of participants never had chemotherapy, 72% never radiotherapy, 81% never targeted therapy, 84% never endocrine therapy, and 17% never surgery. Ten percent each had breast cancer and prostate cancer, respectively, all other tumor types were less frequent. The fatigue prevalence varied from 31% (prostate cancer) to 55% (pancreas cancer), for physical fatigue from 32% (prostate cancer) to 52% (each liver and stomach cancer), for emotional fatigue from 30% (prostate cancer) to 49% (pancreas cancer), for cognitive fatigue the data were nor reported in detail. The authors discuss that (quote) "*Differences between entities were not fully explained by sex, age, BMI, or type and timing of cancer therapy.*" With regard to the (quote) "*considerable observed physical fatigue*

prevalence of 40% among breast cancer patients about 2 years after diagnosis" the authors compared their data as consistent to other authors, and also that (quote) "*an effective fatigue management and treatment is not yet established.*"

However, based on the concept of an "invisible disability" associated with anticancer treatment and possibly only partially reversible toxicities, the expectation that fatigue (in this study measured by the 12 item EORTC-QlQ-FA12 questionnaire lacking assessment of impact of fatigue, like the BFI) will disappear after 2 years with an effective fatigue management is probably not justifiable.

In this study, unfortunately, no data is reported, whether patients had after 2 years still active cancer disease or not. Overall, the majority of the population included had surgery (83%), but only minorities systemic anticancer treatment or radiotherapy. Nevertheless, this study reports clearly that cancer patients have significantly more fatigue compared to an age- and sex-matched "healthy" control, suggesting the suffering and the need to act as professionals.

To explore the question if distinct **trajectories of fatigue** can be identified in women with early-stage breast cancer from diagnosis into survivorship—with the option to identify **risk factors for fatigue**—a longitudinal study followed 270 women five times for 18 months [29] (at baseline [before the onset of adjuvant therapy]; posttreatment [post-tx; after the completion of radiotherapy and/or chemotherapy, if received]; and the 6-month, 12-month, and 18-month posttreatment follow-ups). Sixty-four percent of patients did not receive chemotherapy, whereas 69% received radiotherapy. Assessments included the MFSI-SF (Quote) "*Fatigue was assessed using the General Fatigue subscale of the Multidimensional Fatigue Symptom Inventory–Short Form (MFSI-SF), which assesses the degree to which respondents felt tired, worn out, sluggish, fatigued, run down, and "pooped" within the past week.*" Assessments for **potential risk factors** included pre-cancer medical comorbidities (Charlson Comorbidity Scale), history of childhood maltreatment (Childhood Trauma Questionnaire), major depressive disorder (interview—SCID), depressive symptoms (CES-D), sleep quality (Pittsburgh Sleep Quality Index), and cancer-related distress (Impact of Event Scale). Growth mixture modeling (latent class mixed models) was applied. As main results (quote) "*Five trajectory groups were identified, including "**Stable Low**" (the largest group; 66% of the sample), "**Increasing**" (9% of the sample), "**Reactive**" (8% of the sample), "**Decreasing**" (4% of the sample), and "**Stable High**" (13% of the sample).*"

The Stable Low group women (quote) "*reported low levels of psychological distress, including depressive symptoms and cancer-related distress,*" but "*55% reported clinically significant sleep disturbance.*" The Stable High group was considered a high-risk group with high baseline fatigue levels (three times higher than Stable low and non-cancer controls), and high levels of psychological distress, interview-based history of major depressive disorder prior to their diagnosis of breast cancer (44%) and clinically significant sleep disturbance (97%). In this study, chemotherapy did not differentiate among the fatigue groups, but only one-third got chemotherapy. Women with high odds of not recovering from fatigue had elevated baseline fatigue (78%), and a preexisting history of depression as well as elevated symptoms of depression, distress, and sleep disturbance.

This study supports important risk factors for developing and maintaining CtrF.

Risk Factors for Developing or Maintaining CRF

- Depression
  - depressive symptoms (e.g., BDI-II scores suggesting mild, moderate, or severe depression), low optimism [30]
  - History of major depression (interview-based, SCID)
- Past and recent traumas
  - History of childhood adversity [31]
  - Cancer-related stress, nonacceptance of disease [32]
- Anxiety
  - Fear-of-recurrence
- History of lifetime stress exposure (e.g., divorce, losses, illness, literacy, precarity) [33]
- CINP (chemotherapy-induced neuropathy)
- Chronic pain syndrome
- Active tumor disease [34]
- Obesity and low physical activity [35]
- Preexisting malnutrition or cachexia [36]
- History of sleep disturbances [37]
- Intensity of causative factors for CRF
  - Major surgery
  - Radiotherapy [38]
  - Chemotherapy [39]
  - Targeted, endocrine and/or immunotherapy [23, 40]
- History of elevated fatigue levels before anticancer treatment [41]

For the management of patients, it matters to understand risk or contributing factors in order to tailor specific interventions.

Causes for CRF

The causes for CRF are multifactorial [42]. Evidence is increasing for associations of CRF [43] with

- **Mitochondrial** dysfunction (involving mitochondrial DNA, structure, oxidative pressure, and alterations of ATP metabolism) [21, 44, 45]
- **Skeletal muscular** dysfunction (mitochondria, myogenesis, muscle mass, etc.) [46–48]
- **Inflammatory system dysregulation** (pro-inflammatory and anti-inflammatory cytokines peripherally and in the CNS [49], inflammatory adipokines, etc.) [50–60]
- **CNS and endocrine function disorders** (neuropeptide, neurotransmitter, HPA axis dysfunction, 5-HT3 neurotransmitter deregulation, circadian rhythm dysfunction) [61, 62]

- History of **psycho-neurological symptoms** [63]
- Vagal afferent activation and autonomic dysfunction (e.g., advanced cancer [64])
- Alteration of the gut microbiome [65, 66]

Also **genetic alterations** and polymorphism were reported to be associated with the development of fatigue [67–72].

Currently, no cause of CRF is sufficiently understood to serve as a diagnostic measure accepted by health authorities to diagnose unequivocal CRF.

Diagnosis of CRF

For the diagnosis of CRF, a subjective experience of the patient, a fatigue assessment tool has to be given to the patient [73, 74].

- *First,* the **silent symptom fatigue** has to be assessed. For this **screening,** a single-item question on perceived severity of fatigue is sufficient, for example, as asked by the ESAS [75].
- *Second,* the **impact of fatigue** on patients' function and quality-of-life shall be assessed. The most frequently used and well-validated tool is the BFI (brief fatigue inventory), which is translated and validated in many languages [76].
- *Third,* to assess the **physical, emotional, and cognitive domain** of fatigue, an appropriate tool shall be used. A simple tool is the SIF (Single-Item-Fatigue), which also explores the impact of sleep on improvement of fatigue [77]. Other tools assessing the multidimensional components of CRF are the ReACT-F [78] or the EORTC QLQ-FA12 [79].
- SIF (Single-Item-Fatigue)
  - Severity
    "How much fatigue (weariness, tiredness) did you feel during the past 24 hours?"
  - Cognitive Fatigue
    "How fatigued do you feel because of 'fatigue in the head,' namely, because you have problems with concentration, thinking, or attention?"
  - Emotional Fatigue
    "How fatigued do you feel because you feel no joy, no motivation or pleasure or because nothing makes sense to you?"
  - Physical Fatigue
    "How fatigued do you feel because you feel no strength, because your body is weak, or your muscles feel weak?"
- *Fourth,* the diagnostic criteria of CRF shall be assessed. This can be done by the **DICRFS** (Diagnostic Interview for Cancer Related Fatigue), which is an interview based on the NCCN diagnostic criteria [80]. In several countries, translations of the DICRFS are in use, for example, in Switzerland.

Diagnostic Interview Guide for Cancer-Related Fatigue

1. "Over the past month, has there been at least a 2-week period when you had significant fatigue, a lack of energy, or an increased need to rest every day or nearly every day?"
   → *if here the answer is NO, patient does not have CRF, otherwise continue*
2. "Did you feel weak all over or heavy all over? (every day or nearly every day?)"
3. "Did you have trouble concentrating or paying attention? (every day or nearly every day?)"
4. "What about looting your interest or desire to the things you usually do? (every day or nearly every day?)"
5. "How were you sleeping? Did you have trouble falling asleep, staying asleep, or waking too early? Or did you find yourself sleeping too much compared to what you usually sleep? (every day or nearly every day?)"
6. "Have you found that you usually do not feel rested or refreshed after you have slept? (every day or nearly every day?)"
7. "Did you have struggle or push yourself to do anything? (every day or nearly every day?)"
8. "Did you find yourself feeling sad, frustrated, or irritable because you felt fatigued? (every day or nearly every day?)"
9. "Did you have difficulty finishing something you had started to do because of feeling fatigued? (every day or nearly every day?)"
10. "Did you have trouble remembering things? For example, did you have trouble remembering where your keys were or what someone had told you a little while ago? (every day or nearly every day?)"
11. "Did you find yourself feeling sick or unwell for several hours after you had done something that took some effort (every time or nearly every time?)"
12. "Has fatigue made it hard for you to do your work, take care of things at home, or get along with other people?"

A score of 6/12 or more is compatible with diagnosis of CRF, when doing the DIRFS repeatedly, many patients learn to cope with the fatigue-disability and answer the questions 4, 7, and 9, and maybe 8 with NO as sign of resilience and adaption.

- *Finally*, as a semi-objective assessment, **neuropsychological testing** can be phenomenons of cognitive fatigue [81].

Based on these assessments the diagnosis of CRF can be made including its impact on patients' function and the main domains (physical, emotional, cognitive).

Management of CRF

The first step in the management of CRF is to assess and treat all reversible causes (see above). This requires a systematic approach, a Phenotype approach grouping the causes according to ● Physical, ● Emotional, ● Cognitive, and ● Mixed fatigue is clinically helpful.

Approach to Fatigue in Cancer Patients:

- Malnutrition: assess nutritional intake and nutrition impact causes, weight loss
- Sarcopenia: age-related, bed rest, corticosteroids, muscle toxicity
- Cancer cachexia: weight loss, anorexia, CRP, tumor activity
- Depression: ESAS, Hospital AnxietyDepression Scale (scores <10, 10–12, >12)
- Uncertainty: illness- and prognosis-understanding
- Pharmacological: history and reality check, opiates, benzos., antidepress., etc.
- Delirium: DOS, other tools, fluctuation during the day
- Cancer-treatment related Fatigue: careful history, DICRFS
- Dehydration: history (urine, oral intake), skin, neck veins
- Electrolyte: Phosphate, Calcium, Na and ev Osmolality, Glucose, ev Mg
- Organ-Function: kidney, liver, heart, lung (RR, O2-Sat)
- Infection: history, dynamics of CRP (double in 2–3 days), ev. ProCalcitonin
- Endocrine: TSH, free Testosterone (male)
- Anemia (Hb < 10 g/dL)
- Sleep disturbances (e.g., symptoms)

After all reversible causes have been assessed and treated, in many patients a CtrF (Cancer-treatment related Fatigue) syndrome is likely and a history is needed to confirm.

Careful History Taking:

- did Fatigue if yes how occur during anticancer treatments?
- (typical G2/3 Fatigue d4-11, etc., worse later cycles)
- often association with *C*hemotherapy-*I*nduced *N*euro*P*athy
- has patient been active physically during anticancer treatment?
- how did fatigue further develop, namely when starting to work?
- evidence for cofactors (see also above)
  - Preexisting psychosocial distress or psychiatric disorder
  - Chronic pain syndrome
  - Lack of personal resources to cope with distress and life-changing events
  - Financial and social (over-) burden
  - Lack of physical activity resources
  - Unhealthy eating habits

Multimodal Management

Typically a multidimensional syndrome like CRF (or like cancer cachexia [82, 83]) requires a multimodal management delivered by a multiprofessional (or even transprofessionally working [84, 85]) team, still with the oncology professional as a key person [4, 86]. Several examples combine interventions, an example from Integrative Medicine is the combination of

- **Psychoeducation** (Focus: Activity and rest, sleep, opportunities, and limits)
- **Exercise** (Focus: Endurance, strength, fun)
- **Mind-body** medicine techniques (Focus: Mindfulness meditation, autogenic training, progressive muscle relaxation, yoga, qigong)
- **Acupressure** and acupuncture (Focus: self-care acupressure)
- **Medication** (Methylphenidate, ev. modafinil, corticosteroid, ginseng, guarana, [mistletoe]) [87].

In this study cancer patients suffering from CRF evaluated the multimodal approach and proposed to escalate components according to the fatigue severity. This concept of increasing the modules according to severity contrasts to a concept of multimodal treatment but with an increasing level of professional involvement and switching from outpatient to more intensive inpatient treatments (to assure interventions intensity and coordination).

An example of multimodal management for all patients is the ***NCCN-guidelines (Version 2015)*** [86], combining

- **education** and counseling of patient and family about fatigue and its **natural history** and the importance of self-monitoring of severity and impact
- **energy conservation** and **distraction** (set realistic expectations, prioritize and pace activities, labor-saving techniques and delegate less-essential activities) supported by a daily and weekly diary
- **physical activity** (3–5 h of moderate activity per week)
- physically based therapies **acupuncture** and **massage therapy**
- **yoga**, muscle relaxation, and stress reduction based on mindfulness
- **psychosocial interventions** (support in coping with fatigue and education about anxiety and depression by (a) CBTs/behavioral therapy, (b) psychoeducational therapies/educational therapies, and/or (c) supportive-expressive therapies
- **nutritional consultation** (no substrate deficits, sufficient protein, adequate hydration, and electrolyte balance)
- **cognitive-behavioral therapy** (CBT) for **sleep** (stimulus control, sleep restriction, and sleep hygiene)
- **pharmacological treatment** in selected patients (e.g., methylphenidate).

The **ESMO Clinical Practice Guideline for CRF (2020)** [4] does not specifically discuss multimodal management but mentions in step III Management a combination of

- Patient and family **education**
- **Physical activity**
- **Psychosocial intervention**
- **Pharmacological** intervention (corticosteroids)

Also, this guideline does only partially discusses different CRF populations in their recommendations. For example, the use of corticosteroids is recommended as

short-term use in metastatic patients however without discussing (as done in the ESPEN Guidelines on nutrition in cancer patients [88] and the ESMO Guideline on Cancer Cachexia[1]) the difference of a cancer survivor with well-controlled incurable disease and advanced, symptomatic cancer patients close to end-of-life. The two clinical trials included symptomatic patients as follows (a) patients having three or more symptoms of 4/10 or higher during the previous 24 h (i.e., pain, fatigue, chronic nausea and anorexia, sleep problems, depression, or anorexia) to (quote) "*ensure that patients were experiencing at least moderate to severe symptoms ofthe CRF clinical cluster*" [89], and (b) "*Patients with cancer with average pain 4 (numeric rating scale [NRS], 0 to 10) in the last 24 hours, with 4 weeks expected survival and receiving an opioid for moderate or severe cancer pain*" [90]. Since corticosteroids decrease muscle mass (and strength) and can deteriorate physical fatigue, their use in cancer patients merits caution and application in patients comparable to those patients enrolled in the two studies.

Multimodal management is also applied in advanced cancer patients with fatigue associated with cancer cachexia.

The still enrolling MENAC trial [91] combines

- **Pharmacological therapy** with nonsteroidal anti-inflammatory drugs and eicosapentaenoic acid to reduce inflammation
- **Physical exercise** program using resistance **and aerobic training to increase anabolism**
- **Dietary counseling and oral** nutritional supplements to promote energy and protein balance

The NEXTAC study [92] is an 8 week educational intervention with three exercise and three nutritional sessions

- **Exercise interventions** combined
  - home-based low-intensity resistance training
  - counseling to promote physical activity based on continuous pedometer use
- **Nutritional** interventions included
  - standard nutritional counseling
  - instruction on how to manage symptoms that interfere with patient's appetite and oral intake
- Nutriceutical intervention with supplements rich in **branched-chain amino acids**

These studies show the combination of exercise, nutrition, and pharmacological/nutraceutical intervention, but lacking psychosocial interventions, even though eating-related distress a reality in patients with advanced cancer [93]. Specific interventions to alleviate ERD were developed and piloted [94] as well as novel multimodal interventions proposed combining supportive, palliative, and nutritional interventions [95].

[1] ESMO Clinical Practice Guideline Cancer Cachexia: ESMO open, in press 2021.

In summary, the **multimodal management of CRF includes as main interventions**

- **Physical exercise**: endurance training, resistance (strength) training, regular physical activity habits
- **Nutrition:** protein-rich, anti-inflammatory, secondary preventive (low carbs, fasting, mediterran, probiotics, organic); individual counseling to change habits
- **MBSR-based stress reduction** and **mind-body interventions**: yoga, body scan, progressive muscle relaxation, QiGong, breathing techniques, mindfulness meditation
- **Psychosocial and creative-therapy interventions**: coping with and grief-work about the fatigue-disability, understanding own (unconscious) emotions. Existential threat and coping processes, dealing with anxiety and depression as well as traumata, supportive-expressive therapy, music and/or art therapy
- **Physically based interventions**: massage, acupressure, compresses, bathing
- **Psychoeducation**, **self-management support,** and cognitive-behavioral therapy for **energy management** and sleep: energy conservation, balance expectations, goals and limits (so called double calman-gap: balance expectations [too high and too low] and reality), set priorities, delegate, sleep hygiene
- **Pharmacological interventions** in selected patients: methylphenidate, corticosteroids
- **Social, vocational, and financial support**: enable reliable return-to-work and return-to-home, utilize available insurance system for financial hardship and precarity

For the different types of cancer survivors the multimodal therapies may differ (Table 11.1): in advanced, incurable cancer patients resistance training and protein-rich nutrition prevails, whereas in cured survivors in the working-age with severe CtrF psychosocial and art therapy interventions prevail as well as endurance training.

The above table is based on clinical experience and by reviewing multimodal interventions and individual therapies by the authors of the guidelines and the author of this chapter. The evidence for multimodal management intervention for CRF and also for combination of single interventions is scarce, one reason is the still insufficient classification of CRF-patients, the variability in assessments, outcomes, and also individual therapies. A meta-analysis of 113 unique studies articles (11,525 unique participants) reported that three or four recommended interventions for CRF were effective during and after primary anticancer treatment: exercise (weighted effect size [WES], 0.30; 69 studies), psychological (WES, 0.27; 24 studies), combined exercise and psychological (WES, 0.26; 10 studies), but not pharmaceutical (WES, 0.09; 14 studies) [96].

Table 11.1 Multimodal management of CRF according to survivor characteristics

	Cured survivor no anticancer treatment	Survivors with **adjuvant** anticancer therapy	**Incurable** survivor with well-controlled metastatic disease
Physical exercise			
Endurance	+++	+++	+
Strength	+	+	+++
Physical activity	++	++	++
Nutrition			
Protein-rich	+	++	+++
Preventive	+++	+++	+
Psychosocial and art therapy			
Disability coping	+++	++	++
Deal wt emotions	+++	+++	++
Existential threat	+	++	+++
Physically based interventions			
Massage	++	++	+
Acupressure	++	++	+
Bathing, etc.	++	+	+
MBSR-based interventions			
Yoga, QiGong, PMR	+++	+++	+
Breathing, Body Scan	++	++	++
Meditation	+++	++	++
Self-management of energy levels			
Expectations/ limits	+++	++	+
Energy conservation	++	++	+
Social and financial support			
Return-to-work	+++	++	+
Financial support	++	++	+

Physical Exercise

The evidence for physical exercise to improve CRF is robust [97]. A consensus statement from a multidisciplinary roundtable judged the evidence that physical exercise interventions show a clear benefit for survivors' fatigue as strong [98].

- Training programs that last at least 12 weeks, engaging in moderate-intensity aerobic training three times per week: **benefits in CRF both *during and after* anticancer treatment**
- **Intensity:** The strongest effect of exercise for moderate- to vigorous-intensity exercise, for low-intensity training effect is weak [99]

- **Duration:** exercise sessions longer than 30 min and programs longer than 12 weeks: likely more reductions in fatigue
- **Amount:** insufficient evidence for a linear dose-response, going beyond 150 min·week-1 of aerobic exercise no increase in benefit
- **Combination aerobic and resistance training:**
  - Moderate-intensity combined aerobic plus resistance training sessions performed two to three times per week may also be effective
  - Twice weekly moderate-intensity resistance training may also be effective particularly in prostate cancer
- **Supervision:** efficacy of exercise for fatigue seems independent of the level of supervision and/or setting. However, a recent meta-analysis of individual patient data reports, that supervised exercise was more beneficial for fatigue [100], patients report that supervision also influenced social, mental, and cognitive factors [101].

The question if all CRF-patients profit equal from physical exercise was examined in an individual patient data meta-analysis of 34 exercise RCT of total of 4519 patients [102]. Patients with worse baseline fatigue and lower physical function seem to have a greater profit. During anticancer treatment effects on aerobic fitness were greater for patients with better baseline aerobic fitness, but benefit for muscle strength was independent of baseline values. After anticancer treatment, only patients with low baseline values benefit from muscle strength.

Exercise is associated in cancer patients with improved cancer-specific mortality [103], improved chemotherapy completion rates and reduced toxicity [104], increased exercise capacity and quadriceps muscle force of people following lung resection for NSCLC [105], reduced hospitalization rates and a positive effect on thrombocytopenia [106] and on anemia [107], and on CINP, balance, and strength [108], among other beneficial effects. Exercise seems a "magic drug" to reverse cancer and chemotherapy disturbed molecular signaling cascades [109]. Exercise in chemotherapy-treated tumor-bearing mice counteracted the chemotherapy and cancer-induced loss of muscle mass and strength, partially rescuing autophagy and mitochondrial function [110].

The evidence for the beneficial effects of adequately dosed physical exercise in almost all life circumstances is increasing, as a recent example it was shown, that athletes have an (unexpected) longer survival [111].

Nutrition

Nutrition intervention in patients with advanced cancer and cachexia-related fatigue is likely to improve muscular weakness and physical fatigue. A systematic review and meta-analysis of 11 studies reported beneficial effects of nutritional interventions on body weight in patients with cancer undergoing chemo(radio)therapy [112]. However, the association of improved body weight and (physical) fatigue was not assessed. Given the importance of inflammation as a cause of CRF, interest

is raising to tackle the immune system by tailored diets [113]. Also, an approach is to improve muscle anabolism by dietary interventions: Few studies showed the possibility of increasing muscle protein synthesis by specific nutriments and/or by increasing amino acids or protein administration [114].

In clinical practice for patients with CRF, an assessment to detect malnutrition and associated deficits (e.g., iron deficiency, low vitamin D or B12, low levels of zinc) shall be done and deficits adequately substituted.

Psychosocial Interventions

From the 34 studies with psychological interventions for CRF analyzed in the recent meta-analysis reporting beneficial effects for CRF [96] 19 studies tested a cognitive-behavioral method, 14 a psychoeducational method, and 1 an eclectic method (a unique combination of psychotherapeutic methods). In contrast, in patients with advanced cancer a Cochrane review of 14 studies involving 3077 patients reports (quote) "*little evidence around the benefits of psychosocial interventions provided to reduce fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent*" [115]. A recent meta-analysis of 22 RCTs of psychosocial interventions in patients with cancer, reported that quality-of-life and emotional and social function improved significantly but with small effect sizes however the term fatigue was not mentioned. It can be hypothesized only that fatigue may improve when emotional function improves [116].

These data support that psychosocial interventions may benefit patients with CRF. However, the current data from clinical trials does only partially explain the clinical experience of the importance of supporting patients in their grief work when realizing that they acquired a CRF-related disability with reduced energy reserves, or when supporting patients to ease the weight from past traumas and often only partially understood emotions. These unexpressed and suppressed emotions may consume energy and deteriorate fatigue. In clinical care, supportive-expressive therapy, coordinated with creative therapies (see below) of writing therapy [117] can contribute to less energy consumption in the often unconscious suppression of emotions and traumas.

Creative Therapies: Art and Music

Creative interventions can support patients with CRF to identify, explore, and understand—often initially unconscious—emotions. A meta-analysis of 8 studies involving 467 patients with CRF reports improved fatigue levels compared to controls, regardless of the frequencies and whether patients consumed precrecorded music or participated in live music [118]. A cross-sectional mixed-methods study of 436 patients compared CRF before and after active (83%) or passive (17%) music therapy [119]. The authors report that (quote) "active music therapy was associated with a 0.88-point greater reduction in cancer-related fatigue (95% CI; $P = 0.006$;

Cohen's D, 0.52) at postsession as compared with passive music therapy when restricting the analysis to patients who rated their baseline cancer-related fatigue as moderate to severe (i.e., ≥ 4; $n = 236$ [54%])". Free-text responses confirmed higher frequencies of words describing positive affect/emotion among active music therapy participants. These results support clinical experience of the effects of music therapy in CRF: (a) passive music meditation is less effective than active group music therapy or individual, single patient music therapy and (b) music therapy can improve CRF through the release of burdensome and heavy (yet unconscious) emotions.

Art therapy is also an intervention to approach emotions and traumas. A systematic review and meta-analysis included 27 studies involving 1576 patients and reported reduced anxiety (17 studies, effect size 0.28), depression (9 studies, ES = 0.23), and pain (8 studies, ES 0.54) and increased QOL (6 studies, ES 0.50), but no significant effect for fatigue was found (7 studies, ES 0.16) [120]. The authors hypothesize that the effects of art therapy may also be mediated by exercise, which the patients also received in addition, blurring the effect of art therapy. With regard to mechanism is hypothesized that engaged participation with painting ("Inner-Correspondence") is a mediator (or mechanism) therefore recently an assessment tool for Inner-Correspondence was validated [121]. These results match only partially clinical experience of the beneficial effects of art therapy specifically in patients with substantial distress associated with traumatic, denial, and unconscious emotions, but also a poor interest in music therapy. Such patients often profit from art therapy.

Body-Based Therapies, Massage

The therapeutic approach in CRF to improve body awareness and body image is different to physical exercise or psychosocial, creative, or MBSR-based interventions. Old data support the possible beneficial effect of touch and massage on CRF [122, 123], as well as from acupressure reported from a small trial [124]. Recent data from non-cancer populations (e.g., after coronary angiography) suggest effects of massage on fatigue [125].

The mechanism of human touch is unclear, one hypothesized mechanism is brain-to-brain coupling, as researched in pain release through touch [126].

MBSR-Based and Mind-Body Interventions

Mindfulness-Based-Stress-Reduction based interventions and Mind-Body interventions encompass various therapies (e.g., yoga, QiGong, meditative breathing, mindfulness meditation, body scan, progressive muscle relaxation) aiming to center the patient to fully present in the present, abandoning distractions, stress, and overactive thinking and planning. The evidence that **MBSR**-based interventions can reduce CRF is growing with reports on the various techniques. A systematic review of

mindfulness-based arts interventions analyzed 13 studies (8 RCTs and 5 quasi-experiments) with however significant heterogeneity of interventions. The results show improved QoL, psychological state, spiritual well-being, and mindfulness, but with equivocal results on CRF [127]. A Cochrane systematic review explored MBSR in breast cancer patients with 10 RCTs and 1571 participants, among them in 5 RCTs with 693 participants it was reported that MBSR probably reduces fatigue (SMD −0.50; moderate-certainty evidence) [128]. Another systematic review and meta-analysis of 10 studies including 1709 participants showed a significant positive effect on fatigue post-intervention, but not a 6 months follow-up [129]. Another systematic review and meta-analysis of 29 independent RCTs of MBIs with 3274 participants included 6 studies with 626 participants which assessed not only psychological distress but specifically fatigue. A significant effect of MBIs to improve fatigue was found ($g = 0.51$; $p = 0.001$) post-intervention but not anymore at follow-up (mean 6.6 months, range 3–24) [130].

A meta-analysis on the effects of **yoga** on pre- to post-intervention improvements in fatigue among cancer patients examined 29 studies representing 1828 patients and found a small, statistically significant (0.45, $p = 0.013$) decrease in fatigue [131]. The yoga type was reported to be a significant moderator of the effect on fatigue, but not session length (in contrast to yoga's moderate effect to improve depression). Another meta-analysis of 17 studies involving 2183 breast cancer patients reports a large effect of yoga on fatigue in posttreatment and a small effect on intra-treatment patients [132]. Supervised yoga class, longer sessions (90 min not 60 min), and a longer duration (8 weeks not 6 weeks) were associated with larger effects of yoga on CRF. The effect was more pronounced in physical fatigue than on cognitive or mental fatigue. These data are consistent with the reported effects of yoga on symptom management in cancer patients [133] and results of clinical trials published after the meta-analysis [134, 135].

Also for **Tai-Chi** a meta-analysis was performed including 3 studies with 234 participants exploring fatigue, where a significant improvement (SMD = −0.37; $P = 0.03$) was reported [136].

In summary, data are quite robust that MBSR and namely yoga improves CRF.

Self-management Including Energy Conservation

Educational interventions amended by support programs are reported to improve CRF. An early trial of 105 women with stage I or II breast cancer starting chemotherapy showed that individualized fatigue education and support programs delivered in the clinic and by phone over three 10- to 20-min sessions 1 week apart improved fatigue [137]. A RCT of 135 breast cancer survivors compared an educational group energy conservation intervention to waiting-list patients and could report that CRF (all domains) was reduced in the intervention group from pre- to post-intervention, and this persisted over the 8-weeks follow-up period ($F = 69.8$, $p < 0.001$) [138]. The energy conservation intervention was (quote) "*a small group discussion consisting of five weekly sessions a 90.0 min for groups of 6–8 breast*

cancer survivors. The intervention guided the participant to have formation of an accurate representation of the symptom of fatigue, lead the development and implementation of a plan to conserve energy, and evaluate the effectiveness of the new efforts. Patients learned to have energy conservation skills, review their daily routines, structure their activities according to their energy levels and utilize a patient diary. Patients discuss the use of resources to overcome barriers that may occur when implementing new strategies into everyday life. Patients share their experiences with the program in everyday life. For homework between sessions, participants monitored their fatigue, sleep, rest, activity, and other symptoms. They assessed their activity patterns by making a list prioritizing their usual activities for one week."

A modern form of self-management is the application of a **mobile app** (Untire), which was examined in a RCT of 519 patients compared to 280 waiting-list controls [139]. The trial reports significantly larger improvements in fatigue severity ($d = 0.40$) and fatigue interference ($d = 0.35$) in app users, with larger effects seen on participants with medium or high app use, but without association to education and cancer stage. The untire app comprises four modules (i.e., My themes, My exercises, Physical activity, and Tips), which is probably effective by (quotes) "*addressing dysfunctional thoughts via CBT and psycho-education (My themes), reducing stress and improves sleep via MBSR (My exercises), help to improve physical fitness through exercise instructions (Physical Activity), and empowering via positive psychology (Tips).*"

The approach to empower patients to monitor energy levels, identify energy-consuming stressors and energy resources, being active in beating fatigue by exercise is a good intervention, but may be improved by adding individual prioritization of energy use, balancing (too high) expectations, and realistic initiatives to set goals to improve reality, and amend the other key interventions for CRF (e.g., nutrition, massage, etc.).

Pharmacological Interventions

Pharmaceutical agents play a minor role in management of CRF, as a recent narrative review focuses on incurable (palliative) patients [140] and also the ESMO CPG on fatigue [4] summarizes.

Corticosteroids are reported to improve CRF in advanced, incurable, and symptomatic cancer patients, but only when given 1–2 weeks [89, 90] or in the terminal stage.[2]

Methylphenidate, a psychostimulants is a "logical" drug to investigate in CRF, several trials have been conducted with mixed results. The most recent trial included 28 evaluable patients with advanced cancer who got methylphenidate or placebo as needed, a significant improvement of fatigue was reported after 2 and 5 h, respectively [141]. This contrasts to another recent double-blind placebo-controlled

[2] ESMO Clinical Practice Guideline Cancer Cachexia: ESMO open, in press 2021.

RCT of 77 patients with advanced cancer, where fatigue improved significantly after 3 days of treatment and was stabilized on day 6, both with placebo and methylphenidate [142]. It can be hypothesized that the intrapatient crossover design [141] is more sensitive to the drug effect. A prior systematic literature and meta-analysis (not including above trials) analyzed 5 RCT with 489 patients and found that the pooled data suggest a mild beneficial effect of methylphenidate on CRF, namely with a slightly longer treatment duration [143].

Ginseng is a phytotherapy with reported potential to improve CRF [144]. A recent systematic review and meta-analysis investigated seven clinical trials and one retrospective study using American ginseng (n = 3), Asian ginseng (n = 3), and Korean ginseng (n = 2) [145]. Unfortunately, the quality of the studies varied greatly therefore the authors conclude (quote) "*Although our findings support the safety and effectiveness of ginseng in the treatment of CRF, the number of high-quality studies is not adequate to adopt ginseng as a standard treatment option for CRF.*"

In summary, pharmacological interventions still play a minor role in CRF, the multimodal management for CRF is key.

Conclusion

Management of CRF requires a proactive screening and structured assessment of all patients with cancer, followed by treatment of reversible causes of fatigue, as basis for multimodal, individualized, and transprofessionally guided intervention package.

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Fertility and Sexuality in Cancer Survivors

12

Margherita Condorelli, Oranite Goldrat, and Isabelle Demeestere

Introduction

Cancer incidence is steadily increasing worldwide. In 2012, European countries accounted for 25% of worldwide cancer burden, with lung, prostate, breast, uterine corpus, and colorectal being the most frequently diagnosed malignancies in men and women [1]. In the pediatric (from birth to 14 years of age) and adolescent and young adult (AYA) populations (aged 15–39 years old), 10,000 and 70,000 new cases, respectively, are reported annually in North America [2]. These include mainly hematological, central nervous system (CNS), colorectal, testicular, and breast cancers [3].

In parallel, overall survival rates have improved over the last few decades, regardless of gender, age, geography, and socioeconomic conditions, thanks to early diagnosis and progress in treatment modalities such as surgery, radiotherapy, chemotherapy, and endocrine and targeted therapies [4]. An increasing number of young men and women worldwide are becoming cancer survivors. In 2019, around 17 million cancer survivors were reported to be living in the United States, with an estimated prevalence of more than 22 million survivors in 2030 [4].

Although multidrug approaches are often the best option, these may induce long-term side effects that severely diminish survivors' quality of life (QoL). Cancer survivors who are of reproductive age form a particular population, with specific

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psychological, social, professional, sexual, and family needs and concerns related to their age at diagnosis [5]. This population copes differently with serious illness as compared to very young children or older adults [6, 7].

Sexual difficulties and/or infertility may occur after cancer therapy, regardless of whether the disease is related to reproductive or nonreproductive organs [8]. Although these issues have long been overlooked by health care providers, they are of critical importance for young cancer survivors and represent high priority and long-term priority concerns. These concerns should be systematically discussed during the acute phase of treatment but also during follow-up. However, healthcare professionals are often focused on patient survival, and discussing these contrasting topics is both difficult and can have a certain "taboo." Nevertheless, over the last few decades, awareness of patient QoL concerns has also increased, leading to the development of several fertility preservation (FP) strategies. International oncological and fertility guidelines strongly advise providing fertility counseling prior to oncological treatment [9–11]. Patients need to be informed of the potential negative impacts of cancer treatment on future fertility and of the existing options for fertility preservation before starting their treatment. Collaboration with fertility centers with specific expertise is required to offer patients access to an appropriate standard and/or innovative strategies in order to safeguard their future reproductive potential.

Gonadotoxicity and Fertility Risk Assessment in Young Cancer Patients

Since the early 2000s, research on treatment gonadotoxicity and on FP has become a priority for a variety of reasons [12]. There has been increasing interest in cancer survivor care and QoL, including fertility in cases involving reproductive age patients. The development of novel therapeutic agents and innovative protocols in oncology, with unknown effects on gonadal function, challenges fertility counseling. Advances in therapeutic options stimulate new clinical and fundamental research that aims to provide additional evidence regarding the possible repercussions of new therapies on reproductive function.

Fertility in young cancer patients is influenced by multiple factors. First, a pelvic or gonadal cancer location can lead to direct damage, due to gonadal surgery and/or irradiation of the reproductive tract for therapeutic purposes. Moreover, indirect damage due to gonadotoxic oncological drugs occurs frequently in young patients with hematological diseases or solid tumors (e.g., breast cancer, sarcoma). Also, cancer itself can cause alterations in fertility parameters, and finally, chronic care with adjuvant therapy may not be compatible with pregnancy. Nevertheless, the occurrence of gonadal insufficiency during and after treatment remains difficult to predict for each individual patient, as it can be transitory. Therefore, it is also important to inform patients about the risk of unexpected pregnancy during and after treatment and discuss the need for contraception [9, 11].

Fertility counseling should take into account the patient's baseline characteristics such as age, ovarian reserve in women (based on antral follicular count (AFC) and

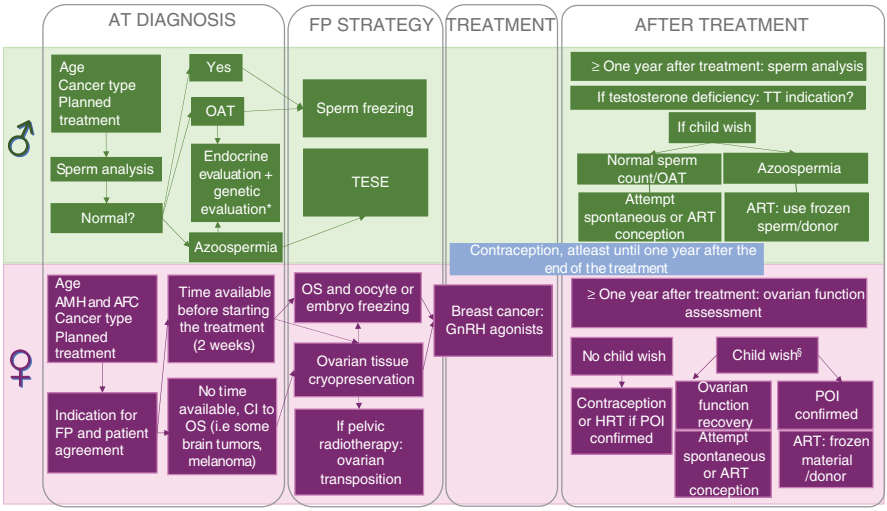

Fig. 12.1 Oncofertility counseling from cancer diagnosis to remission. * can be postponed to the remission period § multidisciplinary approach, involving the oncologist, the fertility specialist, and the obstetrician. Abbreviations: *OAT* oligoasthenospermia; *AMH* anti-Müllerian hormone; *AFC* antral follicular count; *CI* counterindication; *OS* ovarian stimulation; *TESE* testicular sperm extraction, *TT* testosterone treatment, *POF* premature ovarian failure; *HRT* Hormone Replacement Therapy

anti-Müllerian hormone (AMH) value), sperm count in men, and, if necessary, endocrine and genetic parameters (Fig. 12.1). Tumor characteristics, site, prognosis, and treatment should also be taken into account when advising patients regarding an FP strategy. It is also important to recommend a follow-up to evaluate gonadal function recovery at cancer remission. Finally, the presence of predisposing genetic mutations that could potentially affect future fertility should be discussed when appropriate. The consequences of a predisposing genetic mutation for the offspring should be discussed with a medical geneticist as well as the availability of preimplantation genetic diagnosis (PGD) for future embryos.

Gonadal Damage Induced by Oncological Treatment

As summarized in Table 12.1, oncological agents have different gonadotoxicities according to the type and cumulative dose administered [13–15]. In women, an overall negative effect on the chances of becoming pregnant after cancer diagnosis was shown by Anderson et al. in their population-matched registry study comparing 10,271 cancer survivors to 30,811 controls [16]. A drug's impact is commonly evaluated according to the age at exposure (Table 12.1). In men, sperm recovery can occur up to 5 years after the end of therapy, depending on the type of treatment administered [17]. The use of a wide range of therapeutic regimens, as well as multidrug strategies, increase the difficulty of fertility counseling. Moreover,

Table 12.1 Treatment gonadotoxicity

Treatment gonadotoxicity risk	Regimen type
High (80%)	– Alkylating agents based regimens (cyclophosphamide equivalent dose CED >5–8 g/m^2) (Melphalan, Carmustine, Lomustine, Chlorambucil, Procarbazine, Ifosfamide, Busulfan, Nitrogen mustard, Carmustine)
Intermediate (40–60%)	– CHOPP
	– MOPP
	– FEC
	– Actinomycin D
	– Cisplatin/carboplatin
	– escalated BEACOPP (<30 years)
	– Anthracycline-based regimen
Low (≤ 20%)	– Thiotepa
	– Vinblastine/Vincristine
	– Amsacrine
	– Bleomycin
	– Etoposide
	– Fludarabine
	– 6-mercaptopurine
	– Mitoxantrone
	– Thioguanine
	– Interferon-α
	– ABVD
	– 4–6 CHOP cycles
	– Bevacizumab
	– Cytarabine
	– Methotrexate
	– Fluorouracil
	– Taxane
Unknown	– Monoclonal antibodies (trastuzumab, bevacizumab, cetuximab)
	– Tyrosine kinase inhibitors (erlotinib, imatinib)
	– Oxaliplatin
	– Irinotecan

Abbreviations: *TBI* total body irradiation; *CMF* cyclophosphamide methotrexate fluorouracil; *CEF* cyclophosphamide epirubicin fluorouracil; *CAF* cyclophosphamide doxorubicin fluorouracil; *TAC* docetaxel doxorubicin cyclophosphamide; *BEACOPP* doxorubicin bleomycin vincristine etoposide cyclophosphamide procarbazine; *ABVD* doxorubicin bleomycin vinblastine dacarbazine; *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone; *FEC* fluorouracil, epirubicin, cyclophosphamide

information is lacking on the gonadotoxicity of novel therapies, as trials on drug efficacy rarely include fertility parameters in their outcomes.

Radiotherapy has a gonadotoxic effect in both sexes (Table 12.2). In men, it can affect testicular germ cells, the Sertoli cells that support spermatogenesis, and Leydig cells that produce testosterone. Leydig cells are relatively resistant to

Table 12.2 Radiation dose effects on fertility

Radiation dose (Gy)	Effect on the testis	Effect on the ovaries	Effect on the uterus
>0.15	Reversible oligozoospermia		
0.35–0.5	Reversible azoospermia[a] (in 10–18 months)	Very low risk	
≤1.5	Long-term azoospermia (recovery by 30 months)	Low risk if patient is <40 years	
2		Depletion of follicle pool by 50%	
<3		High risk of ovarian insufficiency (60%)	
<5	Azoospermia (recovery >5 years)		
>6	Permanent azoospermia	Sterilizing dose in women >40 years	
Fractionated >2.5	Prolonged azoospermia		
>12	Leydig cell failure and testosterone deficiency		Increased risk of miscarriage, premature birth, and low birth weight
14.3		Sterilizing dose in women >30 years	
16–18		Sterilizing dose in women >20 years	
>18		Sterilizing dose in kids	
>20		Sterilizing dose at birth	
>25 Gy			During childhood, not compatible with future pregnancy
>45 Gy			Not compatible with pregnancy

[a]Recovery does not always occur [13, 21]

radiation, ensuring testosterone production even in cases where azoospermia has occurred [18]. In women, pelvic radiation therapy is mainly applied for gynecological and colorectal cancers. Although colorectal cancer remains rarely diagnosed in patients younger than 40 years old, its incidence is increasing in the AYA population [19]. In women, radiation therapy depletes the ovarian reserve and can permanently damage the uterus. Ovarian exposure to a radiation dosage of 2.5–5 Gy can lead to premature ovarian failure (POF) in 60% of patients. A dose of ≥12 Gy has a detrimental impact on the uterus and is associated with increased risk of miscarriage, premature birth, and low birth weight. It is generally not advisable for an AYA patient to become pregnant if the uterine dose received has been >25 Gy in childhood and >45 Gy in adulthood [13]. However, a case report described a term

pregnancy after multiple ovarian tissue transplantations and recovery of ovarian function in a patient who had received a uterine dose of 54 Gy [20].

Cancers Directly Affecting Gonadal Function

Cancer of the Reproductive Organs in Women

Worldwide, ovarian borderline and epithelial cancers were diagnosed in 30,000 women younger than 40 years old in 2012 [22]. In the last 30 years, fertility sparing surgery (FSS) for young patients of childbearing age has been implemented. This approach allows for the preservation of the uterus and the contralateral ovary (or part of it). It is considered the "gold standard" in patients with early stage malignant ovarian germ cell tumors [23] and has recently been proposed for more advanced stages of the disease [24]. The benefit of using an FSS approach has been debated since the late 1960s in newly diagnosed early stage epithelial ovarian tumors [25], with a multitude of studies showing no detrimental prognostic outcomes using FSS in selected cases. Recent guidelines have included FSS as a treatment strategy in young patients with early stage and low-grade epithelial ovarian cancers, after adequate surgical staging [26, 27]. Nevertheless, disease recurrence has been observed in 11% of cases [28], justifying fertility counseling if having a family is planned in the near future. For more advanced stage disease, the standard approach is recommended, with removal of the contralateral ovary and hysterectomy.

It is also important to mention that in 10–15% of cases, a diagnosis of ovarian cancer is associated with a BRCA1/2 mutation [29]. Even if the patient has undergone FSS, a contralateral risk-reducing salpingo-oophorectomy is advised at 35–40 years old.

Worldwide, cervical cancer accounted for 110,749 new cancer diagnoses in 2012, being the second most common type of cancer in women of reproductive age [22]. In young populations, FSS should be offered for FIGO stage IA1 to IB2, especially when the tumor is $\leq$2 cm and when it is an adenocarcinoma [30, 31]. FSS includes conization or radical trachelectomy, without brachytherapy, according to disease stage. This procedure is not suitable for small cell neuroendocrine tumors, gastric type adenocarcinomas, and for more advanced stages of the disease, which will need a more extensive surgery and/or chemoradiation. Even though trachelectomy is considered to be a FSS, patients have to be informed about possible obstetrical complications, related mainly to cervical factors, with a high risk of miscarriage and premature delivery that will eventually follow the procedure [32]. In the systematic review from Bentivegna et al., prematurity risk was assessed at between 39 and 57%, according to the surgical technique used [32].

Another cancer that should be mentioned because it can affect the uterus in the AYA population is endometrial cancer. Five percent of endometrial cancer patients are less than 40 years old and its incidence is increasing in parallel to endemic obesity [33]. Well-differentiated (grade1) endometrial cancer limited to the endometrium can be treated using an FSS approach (progestin-based therapy associated

with control by hysteroscopy and curettage), but pregnancy should be attempted without delay once remission is confirmed after 6 months of follow-up [34].

Cancer of the Reproductive Organs in Men

Testicular cancer is the most common cancer in young men [22], with a rising incidence worldwide [35]. Five-year relative survival is of approximately 90% [36]. At diagnosis, sperm parameters may already be altered, as the tumor development is intertwined with testicular disorders and has a direct and indirect impact on spermatogenesis [37]. Surgical treatment, chemotherapy, and radiotherapy may further increase infertility risk.

Malignancies Indirectly Affecting Gonadal Function

As already mentioned, cancer itself may have an indirect effect on fertility parameters. Many studies have shown that pretreatment sperm counts can already be impaired by the disease. Recently, a multicenter, prospective, longitudinal study of 45 patients suffering from Hodgkin's lymphoma, 13 from non-Hodgkin's lymphoma, and 29 healthy controls, showed a significant decrease in sperm parameters and a significant increase in aneuploidy at diagnosis in lymphoma patients [38]. Alteration of sperm parameters has also been shown in leukemia patients and testicular cancer patients, and the integrity of sperm DNA was found to be altered in other types of cancer [39]. Conversely, studies on the female cancer population are not conclusive. A recent retrospective study on 992 oncologic patients aged 18–40 years who underwent oocyte cryopreservation from January 2007 to March 2016, showed no difference in age-adjusted oocyte yields according to the oncological disease [40]. In contrast, a retrospective monocentric study conducted between 2000 and 2014 on 306 oncologic patients who underwent ovarian stimulation (OS) for fertility preservation, showed that a significantly higher number of oocytes were retrieved from patients suffering from hematological malignancies and significantly fewer mature oocytes from the group with gynecological malignancies [41].

Fertility Preservation Strategies in Young Adults

Since the early 2000s, there has been an important development in fertility preservation procedures. Even though cryopreservation of gametes and/or embryos is the standard method to preserve fertility, research is also focusing on pharmacological gonadal protection with some promising results.

Oocyte and Embryo Freezing

Oocyte and/or embryo freezing is the first option to be proposed in young women when there is sufficient time before starting treatment and no contraindication to OS

[3, 9, 11]. The time needed for OS is an average of 15 days [42], and the treatment can be started anytime during the patient's menstrual cycle using a random-start protocol [43]. At the end of the OS, mature oocytes are collected and can be either directly vitrified, or fertilized, and the embryos vitrified. Embryo vitrification is an effective technique in this setting [44]. The main disadvantage lies in the fact that embryos are shared between the patient and her partner, making it fruitless if the couple does not last. With the implementation of the vitrification technique, oocyte cryopreservation has been developing its potential, with results that are almost similar to embryo freezing [45]. In a retrospective multicenter study including all 1468 women who underwent oocyte cryopreservation for elective and medical indications between January 2007 and April 2015, 137 patients returned to the clinic to use their oocytes. The survival rate of cryopreserved oocytes to warming was 85.2% (95% confidence interval [CI] 83.2–87.2), and was higher in patients ≤35 years old (94.6%; 95% CI 91.9–97.3) than in patients >35 years old (82.4%; 95% CI 79.9–84.9). The live birth rate per patient was 50% (95% CI 32.7–67.3) in younger patients vs. 22.9% (95% CI 14.9–30.9) in older patients. Using Kaplan-Meier survival curves according to patient age group, the authors showed that a plateau of cumulative birth rate of 85.2% was achieved with 15 cryopreserved oocytes in the younger population, while for the older patients the plateau was achieved with 11 cryopreserved oocytes with a cumulative birth rate of 35.6% [45].

As shown by Cobo et al., oocyte cryopreservation before gonadotoxic therapy in cancer patients is as effective as in healthy women who preserve their oocytes in order to postpone motherhood (elective fertility preservation) [46]. This same group reported results from a recent multicentric retrospective study comparing 1073 women who underwent oocyte cryopreservation for oncological reasons to 5289 women who underwent elective fertility preservation. The study demonstrated significant differences between the two groups in terms of the number of collected oocytes per cycle (9.6 ± 8.4 in the oncofertility group vs. 11.4 ± 3.5 in the elective group), and patient age at the time of the procedure (32.3 ± 3.5 for the oncofertility group vs. 37.2 ± 4.9 years in the elective preservation group). Statistically more patients from the elective fertility preservation group have used their cryopreserved oocytes (12.1% vs. 7.4%). No statistical differences were found in oocyte survival rate (83.9% for elective preservation vs. 81.8% for oncofertility preservation) and in cumulative live births per embryo transfer (35.2% vs. 33.9%). When accounting for FP indication, there was no difference between the two groups in terms of live birth rate (odds ratio [OR] = 1.275 [95%CI = 0.711–2.284]; $P = 0.414$), whereas age ≤ 36 at the time of the procedure was associated with a better outcome (adj. OR = 3.106 [95%CI = 2.039–4.733]; $P < 0.0001$) [46].

If enough time is available, it is possible to perform a double ovarian stimulation that allows more oocytes/embryos to be cryopreserved [47]. The combination of OS with an aromatase inhibitor (mainly letrozole) has been implemented in order to decrease serum estrogen levels in breast cancer patients. This strategy has been shown to be safe, although the number of studies is still limited [48]. In the largest prospective nonrandomized study on this topic, 120 breast cancer patients underwent OS with letrozole and were compared to 217 patients who did not undergo

fertility preservation. In a 5-year follow-up, no statistically significant difference was found in terms of relapse-free survival among the two groups (hazard ratio [HR] 0.77; 95% CI 0.28–2.13; $P = 0.61$) [49].

There have been concerns regarding whether letrozole has a negative impact on oocyte harvest [50]. A recent retrospective trial included 94 breast cancer patients undergoing OS with letrozole and 83 OS without letrozole, regardless of the tumor's endocrine receptor status. The two groups were comparable in terms of fertility baseline characteristics. Serum estradiol levels were statistically higher in the group treated without letrozole (1651 ± 1235 vs. 427 ± 332). Even though the number of oocytes retrieved was comparable in the two groups (13.1 ± 10.0 in the group without letrozole vs. 12.2 ± 8.3 in the group with letrozole), the number of mature oocytes that could be vitrified was statistically higher in the group that received OS without letrozole (10.3 ± 8.5 vs. 7.8 ± 5.3) [51].

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation (OTC) has been recently updated from being an experimental procedure to an established medical practice by the American Society for Reproductive Medicine (ASRM) [11]. This procedure has several advantages: it can be performed immediately after the tumor diagnosis, in prepubertal patients, and in patients that already received first-line chemotherapy [52]. The technique requires ovarian biopsies or unilateral ovariectomy, usually by laparoscopy. The cortex containing the small primordial and primary follicles is separated from the medulla and cut into small fragments before being cryopreserved using a slow-freezing procedure. Vitrification is an emerging promising technique in this field that still must be proven to be as effective as slow freezing in terms of follicular survival, but currently this protocol is not yet standardized, and the number of live births remains very limited [53, 54]. After thawing, fragments are grafted onto orthotopic (residual ovary or in a pelvic peritoneal pocket) or heterotopic (subcutaneous) sites to restore ovarian function [55]. However, oocyte quality may be impaired, and only one pregnancy has been described, so far, at a heterotopic site [56]. In particular, in situations where the patient is a BRCA mutation carrier, the ovarian tissue has to be totally removed after achieving fertility restoration in order to prevent the occurrence of ovarian cancer. Orthotopic sites and, more specifically, the remaining ovaries, are probably most suitable in these cases [57].

Transplantation restores ovarian endocrine function in more than 90% of patients, allowing spontaneous conception and even multiple pregnancies [58, 59]. A recent multicentric study showed that among 1314 patients who underwent OTC before June 2018, 70 decided to attempt tissue grafting. Sixty patients could be included in the study [59]. Among these, 52 had no residual ovarian function before grafting. Menses recovered in 47 out of 50 patients (94%), as one patient could not recover her menses since she had previously been hysterectomized and another one had to undergo chemotherapy shortly after her grafting. Overall, among the 60 grafted patients, 30 had at least one pregnancy (50%) and 25 gave birth at least once

(41.6%). Thirty-three pregnancies were conceived spontaneously. Importantly, 24/60 patients had received part of their chemotherapy before OTC and there were no differences in pregnancy, live birth, and miscarriage rates compared to those who did not receive any treatment before the OTC. The mean age at OTC was 24.17 ± 4.62 years and young age has been identified as a positive success factor. Other previously published series have reported a lower success rate for this technique (~18%). This difference may be explained by the very young age of the studied population at OTC in the study from Shapira et al. [59]. Other studies have described comparable efficacy for this technique to oocyte vitrification in young patients but did not take into account the possibility of having more than one child [60]. The downside of this approach is the potential presence of malignant cells in the grafted ovarian tissue. Specific malignancies that can invade the ovaries like leukemia, Burkitt lymphoma, and ovarian carcinoma have the highest risk of neoplastic cell transmission after grafting [13]. Shapira et al. reported ovarian tissue transplantation in an acute myeloid leukemia survivor. The cryopreserved ovarian tissue underwent a complete evaluation in order to rule out the presence of malignant cells. Not all the evaluations were conclusive, but the couple decided to accept the risk. The patient became pregnant through IVF and delivered at term a healthy baby. Twenty-eight months after the grafting she was disease-free and 10 weeks pregnant by natural conception [61]. Even though this case report suggests the safety of the procedure when the tissue is collected after first-line chemotherapy and carefully analyzed for the presence of residual neoplastic cells, transplantation is still not recommended in this situation outside research protocols, and additional experimental data are urgently needed to guarantee its safety. Alternative approaches to using the cryopreserved ovarian tissue are also under development [59]. Other limitations of ovarian tissue cryopreservation techniques include the surgical and anesthesia-related risks that should be carefully evaluated. The age limit is usually set at 35 years, considering the poor risk/benefit balance in older patients [62]. Nevertheless, the age limit varies from one center to another [59].

Importantly, when there is enough time and no contraindication, these two FP approaches may be combined by starting ovarian stimulation directly after ovarian tissue cryopreservation to improve future chances of conception [62]. Finally, ovarian tissue cryopreservation can be combined with ex vivo immature oocyte collection [63]. These oocytes can be in vitro matured and cryopreserved. However, this technique is still experimental and poorly efficient, although a few pregnancies have been reported.

Sperm Freezing

In pubertal patients, the main option for fertility preservation is sperm freezing via masturbation [9–11]. Two or three samples are usually recommended according to the quality parameters and time available before starting oncological treatment to accumulate an optimal amount of sperm straws [11]. In this indication, it is not mandatory to respect the abstinence period of 48–72 h [64]. Moreover, even

when the sperm quality and quantity are not optimal, intracytoplasmic sperm injection (ICSI) can be performed, using the cryopreserved sperm, to fertilize eggs in the future [65]. Although the procedure is very easy and efficient, efforts should be pursued to discuss this option with all young patients and offer them access to it.

When patients suffer from an unpredictable erectile dysfunction (ED) on the day of sample collection, phosphodiesterase type-5 (PDE-5) inhibitors can be proposed [66]. Finally, in case of anejaculation or azoospermia, testicular sperm extraction (TESE) can be performed [11]. This technique can be combined with orchidectomy in cases of testicular cancer or with other surgery such as central venous access device placement [11].

Other Strategies: Surgical Ovarian Transposition and Ovarian Suppression

Few options are available to reduce the impact of gonadotoxic treatment in oncological patients. These options cannot replace any of the cryopreservation strategies listed above but can be combined afterward. When pelvic radiotherapy is planned, it is possible to perform a surgical ovarian transposition as advised by oncological and fertility scientific societies [10, 11]. This intervention can be combined with OTC and pelvic surgery [11]. There are multiple surgical protocols for performing surgical ovarian transposition, and the outcomes (protection of ovarian function vs chances of natural conception) vary widely among studies [67]. Another promising but highly debated strategy that can be proposed is pharmaco-protection during chemotherapy. The efficiency of gonadotrophin-releasing hormone agonists (GnRHa), such as goserelin 3.6 mg every 4 weeks during chemotherapy, has been evaluated for years with contradictory results [68]. However, the most recent randomized controlled trials (RCTs) in women affected by breast cancer suggest its efficacy in this indication [10, 11]. A pooled analysis of 873 patients randomly assigned to receive GnRHa during their chemotherapy showed a significantly higher number of pregnancies among patient who received GnRHa compared to controls (10.3% vs. 5.5%; incidence rate ratio, 1.83; 95% CI, 1.06–3.15; $P = 0.030$), without a detrimental impact on the disease [69]. However, other trials conducted on lymphoma patients did not show any benefit in terms of ovarian failure after treatment [70].

Reproductive and Endocrine Issues After Cancer Treatment

Following primary therapy, cancer patients may be advised to continue a long-term adjuvant treatment to reduce the risk of recurrences, such as hormonal therapy (e.g., tamoxifen in estrogen receptor-positive breast cancer) or immunotherapy (trastuzumab or pertuzumab in HER2-positive breast cancer). These, and other long-term treatments, are usually not compatible with pregnancy, due to their teratogenic

impacts and/or effects on ovarian function. Hence, information about contraception may be necessary to avoid unintended pregnancies [71]. For women, this means that family planning has to be postponed at the cost of further additional impact on fertility due to aging.

After gonadotoxic cancer therapy, acute or late gonadal dysfunction may be observed in both men and women. In women suffering from premature ovarian insufficiency (POI), hormonal replacement therapy (HRT) is strongly advised, as well as calcium and vitamin D supplementation to prevent osteoporosis. However, several situations could contraindicate HRT, including history of thromboembolic events, liver disease, and hormone-sensitive cancers [72]. Although guidelines generally do not recommend the use of HRT in hormonally mediated cancers, some authors have challenged this statement by using HRT in breast/endometrium and ovarian cancer survivors in specific situations [73].

Although less frequent than POI in women, male cancer survivors can suffer from testosterone deficiency [74]. Testosterone deficiency can increase the risk of developing multiple morbidities, such as hypercholesterolemia, hypertension, peripheral neuropathy, and ED [75]. Therefore, the American Urological Association recommends performing testosterone testing in all patients having undergone chemotherapy and radiation therapy [76]. The benefit of testosterone replacement therapy is not yet clearly confirmed [75, 77]. However, in young symptomatic patients, testosterone treatment could be proposed.

Once in remission, patients desiring to become pregnant should be informed about the potential risk of obstetrical complications and an appropriate follow-up should be offered accordingly. In a registry study published in 2017, 2598 births from AYA survivors were compared to 12,990 controls. The authors found that cancer survivors experienced a significantly increased prevalence of preterm birth (prevalence ratio [PR], 1.52; 95% CI, 1.34–1.71), low birth weight (PR, 1.59; 95% CI, 1.38–1.83), and cesarean delivery (PR, 1.08; 95% CI, 1.01–1.14) [78]. It is important to include in the oncofertility care team the elective collaboration with specialized maternal care obstetricians who are aware of the specific needs of cancer survivors and of their increased obstetric risks.

Cancer and Sexuality

Sexual dysfunctions are common in healthy people and include desire, arousal, and orgasmic difficulties, as well as pain, ED, and premature ejaculation. At least one complaint has been reported by 20–30% of men and 40–45% of women [79]. Several risk factors may induce or worsen symptoms, such as advanced age, cardiovascular disease, diabetes, low socioeconomic status, mental disorders, and being an unpartnered woman [80, 81].

In the cancer patient population, estimations vary from 50–60% to 40–100% of patients experiencing sexual dysfunction(s) during and/or after treatment [82–84]. Sexual difficulties, in general, are complex and most probably multifactorial, even more so in the oncological setting.

Factors Influencing Sexuality

Although older age is commonly associated with a higher prevalence of sexual dysfunction and dissatisfaction, young cancer survivors reaching adulthood are disrupted by cancer and its treatments at crucial change-of-life stages. These events may hamper their maturation process and future long-term well-being. A recent review emphasized the negative impact cancer had on AYA survivors in relation to education level, employment challenges, financial burden, and relationship and intimacy difficulties [6]. In a study comparing 505 young breast cancer patients of 23–45 years to 622 older breast cancer patients that were 55–70 years old at diagnosis, women in the first group reported more depression, fatigue, and poorer body image than their older counterparts. They also feared disease recurrence more than postmenopausal women. When compared to healthy age-matched controls (n = 404), young breast cancer survivors experienced less sexual desire, arousal, lubrication, and orgasms. Sexual dysfunctions were often associated with hypoestrogenic symptoms, such as mood disorders, hot flashes, and vaginal dryness, that are usually due to treatment-induced ovarian damage caused by chemotherapy which, of course, was not observed in the healthy controls. Nonetheless, even in older women, these complaints were less frequent [7]. Moreover, endocrine therapy in breast cancer patients, and especially in young women, may worsen vaginal symptoms and discomfort [85].

Notwithstanding age differences, cancer can also impact sexuality even when organs associated with sexual response are not directly involved. In a recent study, 577 AYA cancer survivors, who were diagnosed in the last 4 years with reproductive or nonreproductive cancers (RC and NRC), were invited to respond to a questionnaire regarding sexual changes and satisfaction as well as supportive-care needs. Of the 424 included women, cancer diagnoses were mainly breast cancer (35.5%), Hodgkin's lymphoma (15.6%), and gynecological cancers (12.1%). Of the 153 men who participated in the study, 32.9% had been treated for testicular cancer, 21.7% for Hodgkin's lymphoma, and 13.2% for non-Hodgkin's lymphoma. One-third of all patients reported sexual dissatisfaction and the need for supportive care, with women displaying lower satisfaction scores than men. Women reported more sexual alterations in cases of RC compared to NRC. However, the satisfaction scores were similarly low, regardless of whether the cancer involved body parts directly related or non-related to sexual response, emphasizing the negative impact that any cancer type and therapy may have on patient sexuality.

In another study, young men diagnosed either with testicular or malignant lymphoma (RC and NRC), both reported sexual difficulties needing assistance, although in a significantly higher proportion in the testicular cancer group compared to the hematological cancer group [86].

One study compared the sexual practices and function of young sexually active male adults who were childhood and adolescence cancer survivors and their siblings. The majority of diagnosed cancers (59%) were NRC, including acute leukemia, malignant lymphoma (Hodgkin's and non-Hodgkin's), and CNS tumors. Ninety-two percent received either no or low-dose testicular radiation (<4 Gy) and

72% received either no chemotherapy (48%) or a maximum equivalent cyclophosphamide dose below 8000 mg/m^2 (24%) [87]. Erectile dysfunction (ED) was reported through the International Index of Erectile Function (IIEF) in 12% vs. 4% of cancer survivors and their healthy brothers, respectively.

Cancer-associated sexual difficulties may arise at any time point, whether at diagnosis, during treatment, or follow-up [88]. In hematopoietic malignancies, sexual difficulties are very common after hematopoietic stem cell transplantation (HSCT). In a 5-year follow-up study following HSCT, 80% of women and 46% of men reported sexual dysfunction, compared to 61% and 21% in female and male age-matched controls. This study well illustrated the impact of cancer treatment but also of gender influence on perceived sexual difficulties [89].

Treatment Impact on Sexual Function

Treatments may impair several physiological systems such as endocrine, vascular, and nervous systems. All of these are necessary for an adequate sexual response, both in men and women. In general, all therapies that induce either hypogonadotropic or hypergonadotropic hypogonadism, such as gonad-damaging surgery, chemotherapy, or brain or pelvic radiotherapy, will potentially lead to loss of sexual interest as well as arousal, pleasure, and orgasm difficulties. Women may experience vaginal dryness and pain, and men may suffer from ED [84].

Adequate pelvic blood circulation and peripheral nerves are necessary for arousal, erectile function, vaginal lubrication, and orgasm (including ejaculation in men). Pelvic surgeries for rectal, bladder, or reproductive-organ cancers often cause vessel and nerve damage and impact sexual function.

In cases of respiratory difficulties following lung cancer treatment, urinary or bowel incontinence induced by pelvic surgery or radiation, the presence of an ostomy, or less common situations, such as graft vs host disease (GvHD), the sexual experience may be considerably more complicated and challenging for patients and their partners. GvHD in men displays inflammatory or noninflammatory skin alterations leading to ED as well as painful intercourse and urinary symptoms. Women with GvHD may also experience urinary difficulties along with vaginal burning sensation and bleeding due to tissue atrophy [90].

Different treatment modalities may influence sexual function in various ways. In a large study on testicular cancer survivors, self-reported ED was compared between patients who had undergone orchiectomy and surveillance only (n = 1098), and either chemotherapy alone or with retroperitoneal surgery (n = 788), abdominal radiotherapy (n = 300), and multiple treatment lines (n = 74). Median follow-up was 17 years. Only partnered patients were invited to complete the IIEF questionnaire regarding sexual desire, erectile, and orgasmic function, as well as overall satisfaction. They also completed questionnaires regarding therapy-related neurotoxicity and anxiety or depression. Reassuringly, most men experienced normal erectile function (85% and 83% in the first 2

groups), and 76% and 70% in the latter 2 groups. The odds-ratio for ED was significantly increased in chemotherapy combined with retroperitoneal surgery (1.8 (95% CI 1.1–2.8)), abdominal radiotherapy (1.6 (95% CI 1.1–2.5)), and multiple treatments (2.4 (95% CI 1.2–5.1)) compared to orchiectomy followed by surveillance alone. Radiotherapy was constantly associated with less satisfaction as compared to other treatment modalities. The authors concluded that this was probably due to nerve and vascular damage caused by surgery and radiotherapy, and not only due to platin-related neurotoxicity that induced erectile or orgasmic, and ejaculatory dysfunctions [91]. Yet, anejaculation (either "dry orgasm" or retrograde ejaculation) is not necessarily associated with absence of pleasure and is accepted over time by many patients.

Similarly, some authors have observed that breast cancer patients who undergo breast reconstruction after mastectomy improve their sexual function, probably due to an improved body image. Unexpectedly, chemotherapy may actually have a higher impact on sexuality than local scarring, especially in young women experiencing chemotherapy-related acute ovarian dysfunction [92], leading, among others, to vaginal dryness and loss of libido.

Cancer diagnosis by itself may be a risk factor for sexual dysfunction. In a Scandinavian study on prostate cancer, patients with localized disease were randomly assigned to radical surgery or watchful follow-up. They were also compared to age-matched healthy controls. Eighty-four percent and 80% of prostate cancer patients in the surgery and surveillance groups, respectively, displayed ED as compared to 46% in the control group [93]. Hypogonadism or anti-androgen therapy given for prostate cancer also inevitably cause low testosterone levels, inducing low libido and ED. However, if most of a man's sexual worries are about erection and ejaculation alterations that may be initiated by treatment, it is important to keep in mind that stress, depression, and performance anxiety will worsen ED symptoms to a higher extent.

For young women who expect themselves to be healthy and desirable, cancer and its treatments disrupt their familiar self-image. They may feel less feminine and attractive, which may influence the way they will take pleasure from their body and interact with others. In the case of breast cancer surgery, modifications in self-perception may arise from the obviously visible alterations, but also from the inevitable loss of tactile and sensual sensations. Breast reconstruction following mastectomy can improve the acceptance of the modified body, but well-being and sexual satisfaction have actually been shown to be preserved in women who took an active part in the decision regarding the type of surgery [94–96], whether conservative or radical. Additionally, a positive body-image perception and sense of femininity or masculinity is complex, and depends on a person's self-confidence before cancer diagnosis.

Thus, several factors may cause sexual difficulties in young cancer survivors besides the disease and treatment themselves. Body-image alteration, chronic fatigue, anxiety, and depression also contribute to a negative self-image and increase conflicts and avoidance behaviors, leading to intimate relationship distress. It is therefore important to discuss with patients the negative impact psychological issues may have on their subsequent sexuality.

"Let us Talk About Sex, Doc"

Discussing sexuality issues with a healthcare provider in the oncology setting is a difficult matter for both patients and clinicians. Some patients may feel embarrassed to talk about what is felt to be "recreational activities" while facing a life-threatening disease. They may wait for their oncologist to raise the topic. On the other hand, clinicians are also uncomfortable talking about sexual issues for which they are not appropriately trained. Discussing sexuality is time-consuming during a clinical consultation, which is already overwhelmed by several other aspects of the treatment and its consequences [83, 97]. A study published in 2003 demonstrated that, although most of the interviewed practitioners (16 doctors and 27 nurses) thought ovarian cancer patients would experience some sexual difficulties and 98% believed sexual matters should be discussed, only 25% of doctors and 19% of nurses actually talked about these concerns with their patients. For some of the physicians, sex was a low priority subject to deal with as compared to survival [98].

A recently published meta-analysis of 29 studies conducted on patient-provider communication about sexual concerns showed that around 50% (60% men and 28% women) recalled a discussion on the negative impact of treatment on sexuality, and only 22% of patients reported receiving treatment options [99]. In a systematic review, barriers to discussing sexual dysfunction in gynecological and breast cancer patients were mainly the patient's own discomfort or their sense that their physician was embarrassed to talk about their sexual problems [100].

In the pediatric and AYA setting, there are also various barriers to discussing intimacy. A study of 22 physicians and nurses undergoing semi-structured qualitative interviews showed that sexual and reproductive health conversations mainly focused on fertility, contraception, and safe sex issues [101].

Patients may themselves somewhat put sexuality aside when diagnosed with cancer, whether they have early, recurrent, or advanced disease [102, 103]. In colorectal cancer, although intimacy remained essential, patients (n = 120 men and women) reported a current and persistent decrease in the importance of sexuality as compared to before cancer [99]. However, regardless of age, nonmetastatic partnered patients rated sexuality as more important than single or metastatic patients.

In a study carried out on 232 breast and gynecologic cancer patients, although 41.6% of women were interested in receiving care regarding sexual morbidity, only 7% actively sought help. Younger patients of 18–47 and 47–55 years were significantly more interested in getting information and advice than women of >65 years, regardless of cancer type, stage, and marital status. However, women treated at least 12 months earlier were more willing to seek counseling than women during active treatment, highlighting their loss of interest in sexuality in the acute phase. This study shows the importance of also raising these issues during follow-up [104].

Caregivers need to be appropriately trained in order to be open to discussing sexual concerns in a similar manner to other cancer-related issues. Patients then feel their difficulties are validated and are less embarrassed to talk about them. Adequate information improves patient knowledge that helps them to be more confident in coping with changes. A pilot study on multimodal intervention in 151

hematopoietic stem cell transplant survivors showed that one-third of patients (n = 50) experienced sexual dysfunction causing distress [105]. These men and women benefited from monthly visits (2–6 times) with a trained clinician who performed a thorough assessment of sexual dysfunction causes, as well as targeted interventions for each patient's needs. Participants reported significant improvement in all sexual domains, including libido, arousal, lubrication, erectile function, orgasm, and pain, as well as in overall quality of life, anxiety, and depression. Interestingly, the clinicians' education was actually quite brief, and entailed reviewing literature about assessment and treatment of sexual dysfunction in cancer survivors, receiving a 2-h training by a sexual health clinic specialist, and 2 days attendance in the sexual health clinic to gain experience regarding these issues. Finally, clinicians should also have the option of referring patients with more complex sexual issues to sexual health specialists for more appropriate follow-up.

A Few Strategies

Couple dynamics also change with a cancer diagnosis. Different intervention strategies have been studied and have been shown to be potentially beneficial for either patients and/or partners. These include, but are not limited to, family-based sessions to help deal with disease and uncertainties, sexual rehabilitation with pharmacological aid for ED, and intimacy-enhancing therapy sessions to improve couple communication [106]. However, as pointed out by the authors, in order to benefit from diverse interventions, a baseline assessment is mandatory to identify distress and/or relationship difficulties and the need for further assistance.

Each person is unique and faces sexuality and cancer differently, according to the disease, its therapies, and their known physio-pathological impact, but also due to personal preexisting factors and resilience. Indeed, the importance and previous personal satisfaction of sexuality, as well as "self-coping response" will influence the situation in a disease context [107]. Being confident in enhancing discussions of relationship and sexual concerns at any time, may actually dedramatize some of the patient's worries, and empower them to actively search for solutions and adapt to life after cancer.

Improvements can result from medical and/or psychosocial strategies (Table 12.3). All these approaches are commonly used in the general population displaying sexual dysfunctions and should be implemented in case of cancer or any other disease that may have a direct or indirect impact on sexuality. Potential complications related to surgery or radiation must be discussed beforehand, specifically arousal function (lubrication and erection) deterioration, along with offering nerve-sparing techniques whenever possible. For men, penile rehabilitation should be performed as early as possible, as tissue elasticity may decrease over time. This may involve medical procedures and regular sexual activity. Sexual satisfaction is dependent on physical as well as psychological responses to sexual activity, and counseling should always take both into consideration in order to improve our cancer survivors' sex life. Furthermore, relationship quality may be negatively impacted in

Table 12.3 General recommendations for sexual and intimacy issues management

Issues	Women	Men
Anxiety and/or depression	Psychosocial counseling Medication	Psychosocial counseling Medication
Intimacy and relationship difficulties	Psychosocial counseling Couple-based interventions	Psychosocial counseling Couple-based interventions
Vaginal atrophy/dryness/pain	Moisturizers (daily/periodic use) Lubricants (use during intercourse) Estrogens (systemic[a] or local) Perineal physiotherapy[b] Dilators	
Erectile dysfunction		Testosterone, if indicated PDE5 inhibitors (daily/on-demand use)[c] Penile injections Vacuum erection device Penile implant
Body-image issues	Psychosocial counseling Regular physical exercise	Psychosocial counseling Regular physical exercise
Sexual desire	Consider testosterone, if no contraindications	Testosterone, if indicated
Overall sexual function and satisfaction	Psychosocial counseling	Psychosocial counseling

[a]If no contraindication
[b]Can be used in case of vaginal atrophy and/or stenosis to regenerate vaginal tissue elasticity and help with intercourse as well as gynecological examinations [85, 108]
[c]Phosphodiesterase-5 (PDE5) inhibitors: are contraindicated in case of nitrate use

partnered patients, highlighting the importance of couple-based support, integrating potentially innovative sexual practices.

Conclusion

Although the prognosis for most diagnosed cancers has improved over the last few decades, cancer remains a major stressful life event at any age. Regardless of individual resilience capacities, young patients have specific concerns that include education, professional, social, and financial independence difficulties, as well as involvement in future relationships, with potential sexuality and fertility-related issues. Crucial guidelines regarding these issues have been published in the last 10 years. It is, nonetheless, once again, important to insist that health care providers should discuss these issues with their patients as soon as possible after cancer diagnosis. Fertility issues and fertility preservation options should be urgently discussed before starting gonadotoxic therapies. Nevertheless, the subject should be raised again after the acute phase, approaching patient perspectives and needs regarding their potential future parenthood.

Talking about sexuality may not be the first priority for many physicians, but this topic should also be considered, especially when cancer treatments are highly likely to have an impact on sexual function. However, specifying treatment side effects only beforehand is not sufficient, as sexual difficulties may occur long afterward. Additionally, in partnered patients, the companion should become an inherent part of the patient's follow-up, and couples' difficulties should be screened and addressed with appropriate specific management. Finally, sex and fertility represent normal and natural concerns for both men and women. They should be regular topics to raise, and oncological teams should be trained appropriately and improve multidisciplinary approaches to help their patients adapt to their new life after cancer.

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Description and Management of Radiotherapy-Induced Long-Term Effects

13

Guillaume Vogin

Introduction, Epidemiology, and Grading

More than 19 million new cases of cancer are diagnosed worldwide each year [1]. Radiation therapy (RT) is involved in about 50% of cures in particular in breast, prostate, cervix, head and neck, lung, and brain cancers, as well as sarcomas [2]. Sixty percent of adults and 80% of children and adolescents treated for cancer heal so that oncologists have to follow more long survivors [3]. The majority of available RT facilities use photons to deliver the treatment plan on a target volume defined clinically or on imaging. Because of the physical properties of photon beams, as well as the infiltrating nature of tumors into the surrounding healthy tissues, uncertainties in the repositioning of the patient, the movement of organs or the tumor during a session or all of the treatment, the radiation oncologist must necessarily include a volume of healthy tissue around the target. This constraint, which cannot be totally reduced, is the cause of the potentially toxic nature of any RT.

The risk and the severity of the sequelae are directly proportional to the dose received for a given volume. Tumor and healthy tissues have their own radiation sensitivities. When prescribing the treatment, the radiation oncologist usually applies constraints on organs at risk (OAR) in the treated volume in order to inactivate the tumor cells with an "acceptable" risk of sequelae on OAR of the order of 5% at 5 years—assuming no particular individual over risk [4].

These recommended doses on OAR are mainly derived from clinical experience accumulated over more than a century of practice and were correlated to dosimetric data to get normal tissue complication probabilities (NTCP) models [5, 6]. In 2010, the QUANTEC group published a meta-analysis of quantitative clinical and

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biological data (often incomplete, including many animal data) from the literature on more than 30 organs and tissues and obtained by means of a dozen mathematical models [7]. We are awaiting more accurate guidelines from big data prospectively collected and pooled with standardized patient- or clinician-reported toxicities events correlated with remarkable values extracted from dose-volume histograms of treatment plans [8].

Overall, 3–5% of adults are estimated to suffer from late toxicity that can cause potentially serious sequelae—in absence of therapeutic deviation [9, 10]. In particular, the incidence of sequelae at least 30 years after diagnosis of cancer reaches a cumulative incidence of 73.4% in pediatric oncology [11]. A cohort of 20,227 5-year pediatric cancer survivors was followed retrospectively (Childhood Cancer Survivor Study). The diagnosis was made between 1970 and 1986. The overall excess mortality in this cohort was 10.8 times greater than in the general population (95% CI: 10.3–11.3). 21.3% of deaths were attributable to late toxicities including secondary cancers (12.7%) considered to be induced by treatment. These toxicities are essentially cardiovascular, renal, endocrine, and musculoskeletal. The incidence of late complications continued to increase with the duration of follow-up without reaching a plateau [12].

However, toxicity prevalence may be underestimated in the absence of systematic dose-outcome correlations collections during the follow-up at populational level, even if prospective clinical-dosimetric databases are emerging integrating patient-reported outcome in addition to the clinician one [13]. For instance, 1785 cancer survivors who had undergone RT reported late effects they were experiencing with an Internet-based tool. Their most common diagnoses were breast (53%), lymphoma/leukemia (10%), GI (8%), and GU (8%) cancers. Median time from diagnosis was 2.3 years. Of the whole cohort, the most common late effects reported were cognitive changes (58%), sexual changes (55%), changes in texture/color of skin (50%), and chronic pain/numbness/tingling (39%) [14].

Ultimately, RT-induced morbidity exposes patients to additional morbidity such as fatigue, pain, esthetic prejudice, depressive, and anxiety disorders as well as an additional financial cost linked to healthcare consumption, discrimination, unemployment, and poverty [15].

These late effects are characterized by a clinical latency during which intricated cellular and tissue events take place. These reactions appear more than 3 months even 6 months after the end of RT—especially in slowly renewing tissues [16]. Various clinicopathological aspects are described: occlusions, stenoses, fibrosis, necrosis, neurodegeneration, atrophy, microangiopathy, endocrine hyposecretion, etc., which can occur in all organs and tissues, and causing often irreversible loss of function in absence of therapeutic deviation [17, 18]. Sometimes consequential late effects may occur in continuation of severe early effects—which will not be detailed here [19].

Furthermore, the functional tolerance of organs to irradiation depends on their ability to continue to function as an entity, and therefore on their functional architecture [20]. Each organ is considered to be made up of subunits with a particular organization:

– tissues with a series structure (spinal cord, digestive tract, nerves): the destruction of a subunit of the organ alters the entire function of this organ. A high dose

delivered on a small volume is toxic, the tolerable dose limit is represented by the (near) maximum dose.
– tissues with parallel structure (lung, kidney, liver, parotid): the organ is made up of independent subunits. The function of the organ is impaired when a number of subunits are destroyed. The tolerance dose depends on the dose distribution within the organ and therefore on the percentage of the organ volume irradiated. In this case, the tolerance dose becomes a continuous function of the volume and a high dose in a small volume is tolerable.

The overall tolerance to irradiation of an organ integrates that of the different tissues that compose it: for example, the esophagus has a mucous membrane (rapidly renewing tissue) responsible for early esophagitis during irradiation, and supporting connective tissue (slow-renewing tissue) which can lead to fibrosis and late radiation stenosis.

The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) is the most widely reported descriptive terminology that can be used to report adverse events. Overall, each adverse event—either patient- or clinician-reported—is classified into five levels of seriousness [21]:

– Grade 1: mild effect (temporary discomfort, malaise, discomfort)
– Grade 2: moderate effect (prolonged discomfort, reversible lesion or impairment, need for medical treatment, temporary disability)
– Grade 3: severe effect (delayed but heavy consequence for the patient, irreversible injury or impairment, permanent disability, risk of life not incurred)
– Grade 4: serious life-threatening effect (short-term fatal consequence for the patient, life-threatening risk)
– Grade 5: death

Pathophysiology of RT-Late Effects

The DNA Damage Response at a Glance [22]

After physical, physicochemical, and molecular reactions, ionizing radiations induce specific damages in the cell compartments—the most critical ones involving DNA. Among them, double-strand breaks (DSB) are complex lesions processed by a series of coordinated events within multi-protein complexes lead by the ATM protein [23]. When DSB occurs, the MRN complex (Mre11/Rad50/Nbs1) is recruited from the damaged DNA site and in turn recruits the ATM protein. Physiologically present in the cell as an inactive dimer, ATM self-phosphorylates at the 1981 serine site, resulting in de-dimerization and activation. pATM then phosphorylates H2AX which recruits several proteins to the damaged DNA site that are subsequently phosphorylated by ATM, including 53BP1, BRCA1, Chk1, and Chk2.

These substrates will then induce cell cycle arrest and the activation of checkpoints prior to DNA repair. *A contrario*, an ATM-dependent apoptosis may occur to prevent the cell from surviving. Along with other proteins, such as GADD45 and p21, the

phosphorylation of p53 disrupts cyclin-Cdk complexes causing the G1/S passage to stop or slow down. Ionizing radiation also causes G2 arrest and the accumulation of cells in the G2-M phase, the magnitude of which is generally proportional to the dose.

Homologous recombination uses DNA from the homologous chromosome as a template to faithfully repair the break. This first specific repair pathway takes place preferentially in the S and G2 phase and depends on RAD51 and BRCA proteins [24]; Nonhomologous end joining (NHEJ) aims to join the flanking DNA strands without filling in the missing genetic information therefore producing a loss of genetic information. Ku80 and Ku70 proteins associate, slide on the DNA to the level of the DSB. DNA-PKcs is then recruited and the trimeric complex plays as a serine-threonine kinase activating ligase IV. NHEJ is the main DSB repair mechanism in humans [25].

Finally, the irradiated cell may either survive with accurate genetic information, or survive with unrepaired lesions in more or less critical genes, or die in the first generation, or even die after several mitoses. Radiation-induced death is the end result of various contributions that can be described as different histological and eventually coexist—such as mitotic death, senescence, and apoptosis [26].

Inflammation and Tissue Reactions [27]

RT-induced fibrosis follows a complex, long latent, and self-sustaining pathophysiology [28]. Tissue remodeling following cell death in critical substructures lead to mesenchymal, inflammatory, and epithelial cells of the microenvironment secrete pro-fibrosing factors such as TGFβ1 causing their (trans) differentiation into myofibroblasts [29]. The latter produces a particular extra cellular matrix in excess [30]. The general mechanisms of inflammation play an important role in these manifestations. In fact, during the first stages, an overproduction of pro-inflammatory cytokines (TNFα, IL1, IL6) occurs [31]. Chemokines are then released, attracting the inflammatory cells into the volume irradiated at high dose.

A disturbance in the management of oxidative stress in the irradiated volume is described [32]. Interestingly, the repair signaling pathways and those of fibrogenesis are interconnected [33].

Cofactors of Toxicity

Individual Radiosensitivity and Radiosensitive Syndromes

The distribution of the individual propensity to develop tissue reactions after exposure to a standardized dose of ionizing radiation in the general population (i.e., individual radiosensitivity—IRS) follows a Gaussian curve [34]. At the left of this curve, the patient may experience unusual severe tissue reactions although their phenotype appears grossly normal.

However, a few very rare hereditary diseases are associated with IRS (Table 13.1). These pathologies most often have an autosomal recessive mode of transmission

Table 13.1 hereditary diseases associated with IRS (individual radiosensitivity)

Disease	OMIM	Involved protein(s)	Role	SF2 (%)[a]	Cancer predisposition	Associated phenotype
Ataxia telangiectasia	208,900	ATM	Recognition, signaling, and repair of DSB	1–5	Lymphomas, leukemias, breast cancer	Ataxia, telangiectasia, immunodeficiency, mental retardation, premature aging, café au lait spots
Nijmegen breakage syndrome	251,260	NBS1	MRN complex	2–6	Lymphomas, gliomas	Microcephaly, mental retardation, short stature, immunodeficiency, infertility
NBS-like syndrome	613,078	RAD50	MRN complex	5–9	Lymphomas	Microcephaly, mental retardation, short stature, immunodeficiency
ATLD syndrome	604,391	MRE11	MRN complex, endonuclease activity	15–40	Lymphomas	AT phenotype without telangiectasia or immunodeficiency
ligase IV deficiency	606,593	LIG4	NHEJ, VDJ recombination	5–9	Lymphomas	Severe Combined Immune Deficiency (SCID), Pancytopenia, Growth Retardation, Facial Dysmorphia
DNA-PKcs deficiency		DNA-PKcs	NHEJ, VDJ recombination	8–20		SCID
Artémis syndrome	602,450	Artemis	NHEJ, VDJ recombination	20–40		SCID, erythroderma, hepato-splenomegaly, lymphadenopathy, alopecia
Cernunnos syndrome	611,291	XLF/Cernunnos	NHEJ, VDJ recombination	20–40		SCID, microcephaly, growth retardation, facial dysmorphia

(continued)

Table 13.1 (continued)

Disease	OMIM	Involved protein(s)	Role	SF2 (%)[a]	Cancer predisposition	Associated phenotype
Omenn syndrome	603,554	RAG1, RAG2	NHEJ, VDJ recombination	30–50		SCID, erythroderma, hepato-splenomegaly, lymphadenopathy, chronic inflammation
X-linked agammaglobulinemia (Bruton syndrome)	300,755	BTK tyrosine kinase	NHEJ, VDJ recombination	30–50		SCID
Riddle syndrome	611,943	RNF168	Ubiquitine-ligase targeting H2A	10–20	Hemopathies	Microcephaly, mental retardation, short stature, immunodeficiency
Cornelia de Lange syndrome	122,470	NIPBL, SMC1A, SMC3, RAD21	Cohesin complex	20–70	Hemangioendothelioma, nephroblastoma	Facial dysmorphia, intellectual deficit, growth retardation malformations of the extremities and visceral (cardiac, renal, etc.), gastroesophageal reflux
Fanconi anemia	227,650	FANC proteins incl. BRCA2	Homologous recombination, cell cycle	20–40	Hemopathies, breast cancer, squamous cell carcinomas (H&N, esophagus, vulva)	Chemosensitivity, bone marrow failure, microcephaly, visceral malformations, growth retardation, deafness, sterility, café au lait spots
BRCA1 syndrome	113,705	BRCA1	Homologous recombination, cell cycle	20–40	Cancers of the breast, ovary, colon, pancreas, prostate	
Progeria (Hutchinson-Gilford syndrome)	176,670	Lamin A	Organization of the nuclear lamina	8–19	/	Premature aging, growth retardation, alopecia, lipodystrophy, scleroderma

Huntington's disease	143,100	Huntingtin	Vesicular transport	18–30	/	Neurodegeneration: chorea, dystonia, coordination disorders, cognitive decline, behavioral disorders
Usher syndrome	276,900	USH proteins	morphogenesis of the stereocilia bundle in hair cells and in the calycal processes of photoreceptor cells	15–20	/	Neurodegeneration: deafness-mutism, retinitis pigmentosa
Xeroderma pigmentosum	278,700	XP proteins	Helicases, nucleases involved in NER	15–30	Skin basal cell carcinoma, squamous cell carcinoma, melanoma	Photosensitivity, genodermatosis, deafness, microcephaly, keratitis, cataracts
Cockayne syndrome	216,400	CS proteins	Helicases, nucleases involved in NER	15–30	/	Photosensitivity, genodermatosis, growth retardation, retinitis pigmentosa, deafness, premature aging
Trichothiodystrophy	601,675	TTD	Helicases, nucleases involved in NER	15–30	/	Genodermatosis, photosensitivity, growth retardation, mental retardation
Gardner syndrome (Familial adenomatous polyposis)	175,100	APC	MMR	20–30	Intestinal cancers, thyroid, osteomas of the skull, epidermoid cysts, fibroids, desmoid tumors	Genodermatosis
Turcot syndrome	276,300	hMSH2	MMR	20–30	Intestinal polyposis, brain tumors—medulloblastomas, hematologic malignancies, colorectal cancer, embryonic tumors, rhabdomyosarcomas	Café au lait spots

(continued)

Table 13.1 (continued)

Disease	OMIM	Involved protein(s)	Role	SF2 (%)[a]	Cancer predisposition	Associated phenotype
Rothmund-Thomson syndrome	268,400	RecQ4	RecQ Helicase	30–50	Sarcomas, osteosarcomas	Genodermatosis, premature aging, telangiectasias, hyper- and hypopigmentation, congenital skeletal abnormalities, growth retardation
Werner syndrome	277,700	WRN	RecQ Helicase	30–50	Sarcomas, osteosarcomas, melanomas, thyroid cancer	Genodermatosis, premature aging, bilateral cataract, growth retardation, chemosensitivity
Bloom syndrome	210,900	BLM	RecQ Helicase	30–50	Sarcomas, all carcinomas, leukemias, lymphomas	Genodermatosis, chemosensitivity, photosensitivity, telangiectasia, dwarfism, infertility, café au lait spots
Seckel syndrome	210,600	ATR	Cell cycle, SSB, and replication forks repair	60–80	/	Marked microcephaly, mental retardation, primordial dwarfism, facial dysmorphia
Type 1 Neurofibromatosis	162,200	Neurofibromin	Ras inhibitor	30–60	Neurofibromas, MPNST, gliomas	Cafe au lait spots, genodermatosis, Lish nodules
Basocellular naevomatosis (Gorlin syndrome)	109,400	PTCH1	Sonic Hedgehog receptor (development)	80–100	Medulloblastoma, basal cell carcinoma, breast cancer, colon cancer, odontogenic keratocystic tumors	Genodermatosis, macrocephaly, skeletal abnormalities
Dysplastic nevus syndrome (FAMM)	155,600	p16 and p14ARF	Cell cycle regulation	80–100	Melanoma, pancreatic cancer, breast cancer, myeloma	Genodermatosis

Lewandowsky and Lutz dysplasia or epidermodysplasia verruciformis	226,400	EVER1, EVER2	Membrane proteins involved in zinc homeostasis (HPV barrier)	80–100	Skin cancers	Genodermatosis
Dyskeratosis congenita	615,190	RTEL1	Helicase 1 regulating telomeric elongation	80–100	Squamous cell carcinomas (H&N, esophagus, vagina, or cervix)	Genodermatosis, premature aging, tear atresia, infertility, growth retardation, microcephaly, immunodeficiency, bone marrow failure, cerebellar hypoplasia
Down syndrome	190,685	DSCR1 and DYRK1A	Inhibit the nucleoshuttling of NFATc transcription factors, which regulate development	80–100	Myeloproliferative syndromes, leukemias	Premature aging, mental retardation, heart and digestive malformations, growth retardation, microcephaly, hypotonia
Klinefelter syndrome	400,045			80–100	Masculine breast cancer	Premature aging, infertility, delayed puberty, gynecomastia, tall stature
Hereditary retinoblastoma	180,200	RB1	Negative cell cycle regulator (E2F)	80–100	Retinomas, retinoblastomas, sarcomas	
Li Fraumeni syndrome	151,623	P53, CHK2	Apoptosis, cell cycle, DNA repair	80–100	Breast cancer, glioma, acute leukemia, soft tissue sarcoma, osteosarcoma, adrenal cortex carcinoma	

[a]SF2 stands for surviving fraction after 2 Gy; marker of individual radiosensitivity; the lower the value, the more radiosensitive the individual (normal value >80%)

[35]. Various phenotypes are described—sharing a poor tolerance to RT reflected by a poor SF2.[1] They are associated with abnormal DNA damage recognition or repair, induced either by chemotherapy—or RT. NHEJ defects would rather be associated with a strong immunodeficiency and a moderate to strong IRS while homologous recombination defects would rather be associated with a strong predisposition to cancer and a moderate to weak IRS. The human syndrome associated with the strongest IRS is homozygous ataxia telangiectasia [36]. One percent of the world's population carries heterozygous ATM mutations leading to a weaker but still significant IRS [37, 38].

Comorbidities

Some acquired conditions such as HIV infection [39], *diabetes mellitus* [40], obesity (bolus effect) [41], anemia, tobacco misuse, or systemic inflammatory diseases including connective tissue and inflammatory bowel diseases [42] may confer a slightly increased sensitivity to ionizing radiation due respectively to immunodeficiency, microangiopathy, or the development of autoantibodies directed against DNA repair proteins [43]. Systemic scleroderma and fibrosing diseases in general, such as idiopathic retroperitoneal fibrosis, on the other hand, are very high-risk clinical situations with cases of lethal complications post-RT repeatedly described in the literature [44].

Age

Individual sensitivity to radiation toxicity is a function of the developmental dynamics of the organ, its renewing potential, and ultimately the extent to which it has senesced [45]. Growing organs and tissue in children may suffer from particular reactions compared to adults [46, 47]. At the other end, the susceptibility to late effects in the elderly seems to involve not only a decline in wound healing but also a shift in the mechanisms of radiation-induced cell death toward senescence, interconnected with effects of comorbidities frequent in this age group.

Therapeutic Parameters

Several therapeutic parameters are related to an increased risk of radiation sequels. Due to the deterministic nature of non-carcinologic normal tissue effects, the total dose delivered is a major determinant of outcome. The variations in dose per session have a major impact on late effects—hypofractionation being much more toxic than

[1] SF2 stands for surviving fraction after 2 Gy; marker of individual radiosensitivity; the lower the value, the more radiosensitive the individual (normal value >80%).

the conventional fractionation for the same endpoint and the same volume of irradiated tissue [48]. In the same order of ideas, high dose rate and low interval between fractions (inferior to 6 h) may lead to an increased late toxicity by saturating DNA repair mechanisms in healthy tissue [49].

Severity of Early Toxicity

In mixed organs in which a barrier protecting two components with different renewing patterns is disrupted following RT, early toxicity may directly progress into late effects in the underlying tissue without healing (e.g., epithelia) [19].

Previous/Concurrent Treatments

Associated treatments may alter the cell and tissue response to IR. Several examples can be given with concurrent chemotherapy in lung, breast, or cervix cancer [50, 51]. Concurrent endocrine therapy may also be associated with an increased late radiation toxicity, e.g., lung fibrosis and subcutaneous fibrosis with tamoxifen or late gastrointestinal and genitourinary toxicity with androgen deprivation in men [52]. While often the combination was tolerated well, increased toxicities have repeatedly been reported with some targeted therapies [53] (e.g., erlotinib, bevacizumab and erlotinib, bevacizumab and oxaliplatin, BRAF inhibitors). Finally, checkpoint inhibitors may lead to a higher incidence of immune-related pneumonitis in lung cancer patients who previously received RT [54].

A recent surgery including reconstructive can also affect the late tolerance of RT.

Clinical Description of "Deterministic" Late Effects

A variety of late reactions can occur months to years after initial RT in the irradiation field. All of these reactions generally share the same pathophysiology [17, 27]. Their probability of occurrence as well as their severity are proportional to the dose received by the OAR. As these effects are predictable, they are named "deterministic"; these rules define the prescription constraints commonly applied routinely to OAR (organ at risk). We review them in Table 13.2 [55].

Ubiquitous Late Effects

Skin and Esthetic Sequelae

Three stages of increasing severity but decreasing probability are described:

- Radiodystrophy associates depilation, pigmentation disorders, telangiectasia, atrophy, and skin dryness.

Table 13.2 dose tolerance of the main OAR (organ at risk) in relation with late effects

OAR	Main late effects
Radiosensitive OAR (endpoint occurring with probability >5% for dose usually <20 Gy)	
Ovary	Infertility, temporary or permanent castration
Testis	Temporary or permanent infertility
Lens	Cataract
Breast	Breast atrophy
Growth plates	Growth retardation or arrest
Kidney	Nephritis
Liver	Hepatitis
Salivary glands	Temporary or permanent xerostomia
Bone marrow	± deep/prolonged aplasia
Mild sensitive OAR (endpoint occurring with probability >5% for dose usually 20–60 Gy)	
Lung	Lung fibrosis—respiratory failure
Larynx	Dysphonia
Heart	Constrictive pericarditis, coronary artery stenosis, myocardial fibrosis, valvular damage
Small bowel	Radiation enteritis, occlusive syndrome, perforations, fistulas, malabsorption
Stomach	Late gastritis, ulceration, antral stenosis
Spinal cord	Late radiation myelitis
Hair	Depilation
Rectum	Late proctitis, ulceration, perforation, fistula
Bladder	Radiation cystitis, micro bladder, ulceration, perforation, fistula
Brain—nerves	Brain radionecrosis, leukoencephalopathy, Radiation dementia, Neurocognitive disorders, radiation plexitis, neuropathy
Retina	Radiation retinopathy
Thyroid	Hypothyroidism
Inner ear	Sensorineural deafness
Middle ear	Conductive deafness, chronic otitis media, eustachian tube pathology
Esophagus	Late esophagitis, ulcerations, fistulas
Mucosae	Mucositis, ulcerations, perforation
Skin	Radiodystrophy, Sclero-atrophic radiodermatitis, ulcerations
Radioresistant OAR (endpoint occurring with probability >5% for dose usually >60 Gy)	
Uterus—vagina	Endo-cervical canal stenosis, uterine corpus fibrosis—infertility, vaginal synechiae, ulcerations
Bone	Osteoporosis, fracture complications, osteonecrosis
Muscles	Muscle fibrosis
Joints	Ankylosis
Main arteries	Postradic arterial disease, moya-moya vasculopathy
Connective tissues	Fibrosis

- Sclero-atrophic radiodermatitis with intense tissue sclerosis; retraction and adhesions on the deep planes are responsible for deformation of the area, sometimes associated with pain, which can be intense. Neuropathic pain in the irradiated territory described as burning sensations are fleeting, intense, and favored by the slightest skin stimulation, they are often difficult to control.

- Late radio necrosis corresponds to deep and painful ulcerations occurring on minor trauma.

Late Radio-Mucitis

Late radio-mucitis associates discoloration, thinning, and decreased flexibility of the mucosa and induration of soft submucosal tissues associated with telangiectasias.

It can also be complicated by ulcerations or even necrosis, exposing the soft tissues and underlying bone parts.

Soft Tissue Fibrosis

Fibrosis manifests itself as a decrease in the elasticity of soft tissues. Aspecific, it can develop in all regions of the body.

Muscle Fibrosis

Loss of muscle flexibility with contractures linked to myositis may develop. When it affects the masticatory muscles trismus which can then progress to a permanent constriction of the jaws with an inter-incisor space of less than 35 mm. Ankylosis of the temporomandibular joints can reinforce this trismus. This condition can interfere with the patient's diet, oral hygiene, and communication.

Osteo-articular Effects

Exposure of large bony volumes to high dose RT may lead to osteoporosis, fracture complications, and osteonecrosis (femoral head). Medullary aplasia appears for milder dose over 40 Gy.

Osteoradionecrosis is a particular effect that deserves a deeper description provided further.

Organ/System-Specific Late Effects

Cardiac Toxicity [56, 57]

Cardiac toxicities can take several aspects in order of frequency:

- chronic pericarditis with pericardial effusions or even simple thickening detected by ultrasound. The specific prevalence is 5% if the pericardium received more than 40 Gy, with a correlated mortality of 1% for this dose.
- coronary ischemia resulting from injury to the intima of the coronary arteries (incidence of clinical involvement: 5–10%, death rate from infarction = 5% if risk factors). The distribution of arteries affected by RT reflects the dose distribution. The left anterior descending and the right coronary arteries are most often affected in patients receiving RT for Hodgkin lymphoma, and the left anterior descending artery during treatment for left-sided breast cancer.
- Myocardial fibrosis can alter cardiac compliance, leading to diastolic heart failure if dose >50 Gy

– after mediastinal irradiation fairly frequent valvular damage if >30 Gy (incidence of mitral or aortic insufficiency: up to 15–30%, mortality rate = 0.3%)
– Fibrosis in the conduction system can predispose to conduction disorders (5%)

Cardiac toxicity is potentiated by other cardiotoxic drugs such as 5FU, taxanes, or anti-HER2.

However, the meta-analysis, covering the American registry of 300,000 women treated for breast cancer between 1970 and 2001, shows a gradual decrease in the incidence of cardiotoxicity with new technologies (1990–2000) [58]. Uncertainty remains in specific toxicity induced by the internal mammary chain irradiation.

Pulmonary Fibrosis [59]

Often asymptomatic, late radiation pneumonitis promotes secondary infections. They are quite obvious at the radiological level leading to an interstitial syndrome instead of radiotherapy fields. More rarely (especially if the acute pneumonitis has been severe), chronic respiratory failure and right heart failure by chronic *cor pulmonale* can threaten the ventilatory function of patients.

Upper Limb Edema

After axillary radiotherapy, its definition was a difference of more than 2 cm in the diameter of the arm or forearm between the treated side and the contralateral arm. Its classic incidence is 8% in the event of a combination of extensive axillary dissection and radiotherapy of the axillary cavity. But in case of dissection alone or axillary radiotherapy alone, its incidence is 2%. As the dissection has reduced in height and the lymph node radiotherapy no longer includes the top of the axillary hollow, the incidence should further decrease with little or no symptomatic forms.

Without true lymphedema of the upper limb, pain in the upper limb often persists (especially after lymph node dissection), which may be accentuated by sustained muscular effort.

CNS Late Toxicity [60, 61]

Neurocognitive Disorders

RT causes frequent cognitive impairment. The most frequently encountered problems relate to disorders of attention, memorization, and overall intellectual development. The evaluation of neurocognitive sequelae is difficult since the educational and socioeconomic level intervenes.

These manifestations appear 6–12 months after the end of radiotherapy. The signs are variable and may result in

– Disturbances in attention, comprehension, or cognitive disorders,
– Learning difficulties,
– A decrease in intellectual capacities,
– Disorders, especially, of memory.

The most vulnerable patients are children under seven and the elderly.

Development is gradual, with no return to the previous cognitive state. There is not always a parallel between lesions on MRI and clinical involvement. Treatment can be implemented by the medical team.

Brain Radionecrosis

Cerebral radionecrosis is a vascular lesion of the white matter, developing in the irradiation field, secondary to chronic inflammation of the brain parenchyma, with a tendency for spontaneous extension. Its pathophysiology is not yet clear. Several hypotheses have been put forward: initially vascular or glial damage, chronic inflammation, and role of the immune system. The symptoms of radionecrosis are those of a nonspecific intracerebral expansive process. A seizure is inaugural in half of the cases, signs of intracranial hypertension and a progressive deficit syndrome (sensory, motor, or aphasia) are frequently present. The semiology often reproduces the initial signs of the primary tumor. In pituitary tumors, lesions preferentially affect the chiasma and the optic nerves causing severe visual disturbances; damage to the temporal, frontal, and hypothalamus lobes is often associated, causing cognitive impairment. The clinical and radiological characteristics of radionecrosis are finally very similar to that of tumor progression, making the discrimination of these two entities very difficult. The gold standard for the diagnosis with certainty is pathological analysis. On histological analysis, 50% of lesions are pure radionecrosis, the remaining 50% associated with radionecrosis and tumor cells without predicting their viability. The MRI shows a persistent central hypointense and an enlargement of a preexisting enhancement in T1 gadolinium associated with a hypersignal in T2 with an appearance of "Swiss cheese" or "soap bubble." Perfusion MRI, spectro-MRI, and PET amino acid imaging may provide additional arguments. Other avenues are showing interest in the differential diagnostic strategy—notably radiomics.

Cognitive Impairment Without Dementia: Leukoencephalopathy

After panencephalic irradiation, nearly half of patients present with intellectual disorders 2 years after radiotherapy, mainly relating to attentional functions and short-term memory. The MRI sometimes shows white matter abnormalities in the form of T2 hypersignals and atrophy. The periventricular areas and the deep hemispherical white matter are most often affected. The risk is increased if treatment with Methotrexate is combined with radiotherapy.

Radiation Dementia

The clinical picture is stereotypical although not specific. The first symptoms are insidious. At the initial stage, it is an intellectual slowdown, impaired concentration, and memory impairment predominant in recent events. At a more advanced stage, cognitive disorders are more severe, characterized by apragmatism, diffuse memory disturbances, impaired judgment and reasoning, and mood disturbances. The instrumental functions (praxic, phasic) are however preserved for a long time. The neuropsychological picture thus produces a picture of "subcortical dementia." Other manifestations may be encountered at this stage: gait disturbances with instability

and retropulsion, extrapyramidal syndrome with akinesia and rigidity, resting and/or attitude tremor, pseudobulbar syndrome, epilepsy, incontinence. Brain imaging shows cortical atrophy that is rarely isolated, as it is most often associated with white matter abnormalities as well as ventricular dilation. T2-weighted hypersignals can spread throughout the hemispherical white matter (leucoaraiosis). The evolution is pejorative after grabatisation.

Radiation Cystitis [62]
The clinical signs of late manifestations of bladder lesions vary according to the dominant clinical form: cystalgia, pollakiuria, urgency, and isolated voiding disorders. However, the classic picture that dominates is that of recurrent hematuria, in abundance and variable frequencies up to bladder clotting with retention of urine.

In its more severe form, it may be called "small bladder" syndrome. It results clinically in intense pollakiuria, incontinence, and pelvic pain, which may require a comfort cystectomy.

Urinary incontinence secondary to irradiation of the prostatic urethra and the base of the bladder may also occur.

Late Esophagitis [59]
For a dose >45 Gy over a significant height of esophagus, patients may present with chronic reflux, retrosternal pain, and alterations in peristalsis which may precede stenosis. Dysphagia secondary to stricture or altered motility is caused by fibrosis/muscular damage or nerve injury or odynophagia due to chronic ulceration. Rarely patients may develop a tracheoesophageal fistula and present with dyspnea secondary to aspiration pneumonia. More rarely, perforations and pseudo-diverticula may appear.

Late Gastritis
Patients may present with epigastric pain. These symptoms may be due to nonulcer dyspepsia, late gastric ulceration, or antral stenosis.

Radiation Enteritis [63]
When large volumes of bowel have been irradiated, radiation enteritis can cause wall thickening due to tissue fibrosis and restriction of the lumen of the gut. As a consequence, transit disrupts, and stenosis may result in total occlusive syndrome. Severe tissue ulcerations and necrosis can cause digestive bleeding, perforate the intestinal wall, and create enterocutaneous, enteroenteric, or entero-urinary fistulas. The most common symptoms are intestinal obstruction, malabsorption (marked by acute or chronic diarrhea, nausea, vomiting, weight loss), and, more rarely, abscesses, fistulas, melena. Patients may have bloating, excessive gas, and borborygmi due to small intestinal bacterial overgrowth. Laboratory findings include vitamin B12 deficiency due to small intestinal bacterial overgrowth, and hypoalbuminemia and anemia due to malnutrition or bleeding.

Chronic enteritis accounts for about 10% of the causes of prolonged home parenteral nutrition in adults. Treatment is based on nutritional care, with the correction of malnutrition and deficiencies. Late effects include malabsorption and diarrhea.

Surgery is required in about half of all cases. But surgery is reserved for severe injuries resistant to medical treatment, as mortality is around 15%, and morbidity can go up to 50%.

Late Proctitis [64, 65]
Late proctitis is mainly manifested by red bloodshed from the anus which may be repeated and profuse, sometimes leading to iron deficiency and anemia which may require blood transfusions. The other symptoms are diarrhea, urgent need, tenesmus, or rectal pain. Diagnosis is easily made by examining the rectum during a proctoscopy or colonoscopy which will further rule out another cause of bleeding. The endoscopic appearance of the rectal wall is variable. The mucous membrane may be frosted, whitish, and strewn with telangiectasias taking on the appearance of more or less regular, dilated, and fragile new vessels. It can also be congestive, friable, and hemorrhagic at the slightest touch. In most cases, this endoscopic appearance is sufficiently suggestive that biopsies are unnecessary.

Late Anitis [64]
The most common late complication is anorectal ulceration. Anal strictures (stenosis) or anorectal fistulas may also occur. Patients usually present with anal pain and anal incontinence.

Radiation Hepatitis [66]
A radiation-induced liver disease may occur when the whole liver receives more than 20 Gy or one-third of the liver received more than 40 Gy. The morphologic appearance is that of veno-occlusive disease. The clinical signs typically appear 4–8 weeks after the end of treatment: asthenia with rapid weight gain, ascites, hepatomegaly (jaundice rare during consultation), and hepatic cytolysis.

Nephritis [67]
Clinical nephritis is indistinguishable from renal failure from any other cause, with hypertension, albuminuria, anemia, azotemia, and small atrophic kidneys on imaging. Late nephritis has 5% prevalence 5 years after RT when a dose over 23 Gy was delivered on a single kidney—20 Gy in case of bilateral irradiation.

Ureteral strictures are rare but occur in 1–3% of cases after gynecological treatment involving brachytherapy.

Late Vulvitis/Vaginitis [68]
A late mucositis may occur in the female genital tract leading potentially painful ulcerations, thinning, atrophy, dryness, pruritus, telangiectasias, and dyspareunia. The fibrosis of the subcutaneous tissues drives a loss of elasticity or vaginal synechiae.

Uterine Late Effects
Endo-cervical canal stenosis after endo-uterine brachytherapy, pelvic heaviness and distension with uterine fibrosis and infertility.

Late Radiation Myelitis [69]
The first symptoms appear insidiously in the form of Lhermitte's sign, dysesthesia of the lower limbs with an ascending course. After several weeks, the disorders will worsen and associate with disorders of thermoalgic sensitivity, which are often asymmetric, and with motor, tetra-, or paraparetic disorders. Rarely, the symptoms set in acutely, within hours. The clinical examination finds Brown-Sequard syndrome in half of the cases. Most often, the picture is completed within a few months with the onset of quadriplegia or paraplegia and the onset of sphincter disorders. Sometimes the symptoms stabilize, allowing the patient to remain ambulatory. MRI is not specific: in the acute stage, it may be normal during the first weeks, then show a lesion with T1 hypointense, T2 hypersignal taking up a contrast in a heterogeneous manner, sometimes in a ring and accompanied by perilesional edema; at a later stage, the marrow is atrophic.

Peripheral Neuropathy and Plexitis [70]
Radiation toxicity is related to dose and affects both axons directly and the vasa nervorum, resulting in fibrosis and microinfarction of nerve tissue. Various clinical presentations may occur according to the anatomic territory and corresponding to different damage to nerve roots, nerve plexus, or nerve trunks. Cranial nerve injury predominantly involves the optic nerve. When RT-induced optic neuropathy affects the anterior part of the optic nerve, ophthalmological findings are those of acute ischaemic anterior optic neuropathy with acute loss in visual acuity. However, chronic damage to the posterior portion of the optic nerve or chiasma is the most frequent (posterior radiation-induced optic neuropathy), with gradual impairment of visual acuity. The most serious complication is involvement of the brachial plexus, resulting in disorders of varying intensity, sensory and motor disorders, and even gross brachial plexitis. Clinically, brachial plexopathy starts with subjective paresthesia or dysesthesia which usually decreases with the development of hypoesthesia then anesthesia. Neuropathic pain is generally rare and moderate. Motor weakness is progressive, often delayed by several months, and then associated with fasciculations and amyotrophy. On the other end, delayed progressive lumbosacral radiculoplexopathy is characterized by the absence of sensory signs and paresthesia in contrast to signs of peripheral neurogenic motor involvement, such as amyotrophy and fasciculations. Central signs are lacking, apart from possible associated medullar damage, and the handicap progresses in severity after a few years. Finally, peripheral nerve trunks can be damaged following a RT-induced fibrotic compression—with an aspecific semiology.

Postradic Arterial Disease [71]
Postradic arterial disease of large and medium caliber vessels usually manifests several years after cervical or cerebral irradiation with extremes ranging from

4 months to 24 years and mainly affects patients who were irradiated in childhood. Anatomically, the most common vascular lesions are arterial stenoses or occlusions similar to those of atherosclerosis. Other lesions can be observed: adventitial or periadventitial sclerosis; the primary lesion of the vasa vasorum leading to a modification of elastic fibers and muscle cells, telangiectasias, aneurysm. They are the cause of transient or established ischemic attacks. In the event of cervical irradiation, the lesions involve the primary, internal and external carotid arteries, the subclavian arteries, and more rarely the vertebral arteries. The arteriographic appearance of radiation arterial disease shows several types of abnormalities: stenosis or occlusion of the large extra- or intracranial vessels, Moya-Moya-type collateralization network, more rarely the appearance of diffuse cerebral arteritis, pseudodysplastic segmental dilations, and aneurysms. Located to the Willis polygon, Moya-Moya disease is a vasculopathy with a particular semiology. Patients gradually develop ischemic attacks, epilepsy, motor paralysis, and dementia.

Late Endocrine Effects [72]

Hypothalamohypophyseal insufficiency may be seen after radiation therapy for brain tumor or nasopharyngeal cancer (the hypothalamus is likely to be more radiosensitive than the pituitary). In children, it mainly involves a decrease in the secretion of growth hormone and is clinically manifested as growth retardation. In adults, it is most commonly expressed as hypogonadism and hypothyroidism. Hyperprolactinemia is frequently associated and indicates predominant involvement of the hypothalamus. The disorders are in principle reversible with substitutive hormone therapy.

Peripheral Deficits

Hypothyroidism can occur as soon as the dose exceeds 10 Gy on the gland.

Osteoradionecrosis [73]

Osteoradionecrosis is an exogenous osteitis characterized by a RT-induced bone necrosis which can lead to bone denudation, fistula, or fracture, accompanied by more or less intense pain. Osteoradionecrosis occurs following a mechanical or infectious trauma that offends an already weakened irradiated bone. It mainly affects the mandible, and more particularly the internal cortex of the premolo-molar region and the retromolar trigone. It seems that the risk is greater the closer the tumor is to the bone. A tumor invading the bone would multiply the risk by 4. It is also two to three times higher in patients with dentures.

The initial phase of osteoradionecrosis is very often asymptomatic, causing little pain and reduced functional discomfort.

In more advanced stages, the pain is comparable to that generated by dry socket. Other associated symptoms include dysesthesia, halitosis, dysgeusia, and retention of food in exposed areas.

In the most severe cases, patients will present with epidermal and oral mucositis that will fistulize, with complete denudation of the bone, orostoma, and pathological fractures.

Tooth Decay and Abnormalities [74]

In children, irradiation of the oral cavity causes dental agenesis, arrest of root formation, microdontia, and enamel dysplasia.

Such consequences are not observed in adults, in whom the effects are mainly due to xerostomia, and not to a direct action of ionizing radiation on the teeth.

Clinically, in the irradiated subject, caries begins with an alteration in the color of the teeth, which take on a more or less dark color, generally orange. Deep black "ebony teeth" are quite rare. The process which is responsible for it is poorly explained, different from decay since the resistance of these elements to decay is certain. These "ebony teeth" are characterized by black or dark coloration, the result of oxidation-reduction phenomena resulting from changes in the ecology of the oral environment, but not corresponding to caries damage. Post-radiation caries is localized, initially, on the smooth surfaces of the tooth, whereas in traditional caries, these are respected for a long time because of the salivary protection in a healthy patient. The decay begins electively at the level of the collar and the free edge of the teeth and it causes dentin softening which will result in the partial destruction of the dental crown, giving it the appearance of a tooth constricted at the collar.

Xerostomia

Xerostomia is one of the most debilitating sequelae of head and neck radiotherapy. It makes speech difficult, and food is often only possible without taking fluids. Xerostomia promotes the development of oral yeast infection and dental caries. Dysgeusia is associated with hyposialia. Most often transient but sometimes lasting, it is expressed in two ways: either with the disappearance of the perception of taste or by alteration of the mainly salty or bitter taste.

Otologic Consequences [75]

Late otologic sequels can lead to conductive, sensorineural, or mixed hearing loss depending on the structure involved. When middle ear is concerned, post-RT chronic otitis media and the eustachian tube pathology may lead to conductive deafness. Irradiation alone causes little auditory sequelae up to doses of 54 Gy. On the other hand, the potentiation with Cisplatinum is important and it is preferable not to exceed 45–50 Gy on the hearing organs in case of association.

Gonadal Consequences [76]

In the girl:

Pelvic, craniospinal, and a fortiori total body irradiation can have gonadal and uterine consequences. Ovarian risks start from 2 Gy in total body irradiation and ovarian failure is almost constant after 30 Gy on the pelvis. Irradiation of the flank (e.g., Wilms tumor) at 20–30 Gy does not a priori have any consequences for the ovaries. The uterus is a very radiosensitive organ in young girls. Pregnancies are rare after 10–15 Gy, spontaneous abortions are frequent and low birth weight is the rule.

In the boy:

The germinal epithelium is the most sensitive: doses of the order of 3 Gy cause transient azoospermia. After 12 Gy, azoospermia is often permanent.

Endocrine testicular function is retained up to 20 Gy before puberty and up to 30 Gy thereafter.

Specific Considerations in Pediatrics [77]

Particular clinical entities need to be prevented and watched by the pediatric radiation oncologist:

- the slowing down—or even arrest—of growth linked to (1) the irradiation of the growth plate of the long bones causing a shortening of the limb, responsible for a functional handicap (2) the heterogeneous irradiation of the vertebrae leading to disorders of the vertebral statics. After irradiation of the hip: epiphysiolysis of the femoral head or aseptic osteonecrosis of the femoral head may occur.
- the higher incidence of intellectual sequelae after brain irradiation. The publications of late effects after RT for medulloblastoma showed a delayed, progressive, age- and dose-dependent IQ damage.
- insidious endocrine sequelae after brain or topic irradiations: pituitary, thyroid, and gonadal insufficiency with their specific complications. GH deficiency is the most common complication of irradiation of the hypothalamic-pituitary axis. Pituitary GH insufficiency can occur as early as 20 Gy. Disorders of TSH and ACTH secretion require higher doses of the order of 36–40 Gy.

Clinical Description of "Stochastic" Late Effects

Stochastic effects appear on average much later than the deterministic effects, usually several years after exposure to radiation. The existence of a threshold dose remains debated, that is, a low dose can lead to complication and the severity remains the same regardless of the dose. On the other hand, the probability of occurrence increases with the dose received. A typical example of stochastic effects is second malignancies in the irradiated area. The carcinogenic property of radiation has been well documented through historic studies of exposed pediatric populations for treatment of *Tinea capitis*, hemangiomas of the skin, or atomic bomb explosion.

Even if RT appears justified in terms of cure benefit, 1–2% of the survivors suffer from a secondary radiation-induced malignancy 5–50 years later.

This risk appears to be increased when a large volume of healthy tissue is irradiated and in case of associated chemotherapy (alkylating agents or topoisomerase II inhibitors)—especially in children.

1. Girls are twice as likely as boys. The risk is also greater the younger the child is. Some associations between primary and secondary entities have been described, e.g., hereditary retinoblastoma, Hodgkin's disease, and soft tissue sarcomas. Genetic predispositions are reported: Li Fraumeni syndrome, Von Lippel-Lindau disease, and neurofibromatosis are associated with an increased risk of second cancers.

Table 13.3 Second cancers depending on the radiotherapy applied to the first primary

Primary	Second cancer whose risk appears increased	Dose-dependence relationship
Hodgkin lymphoma	Breast, lung, ENT, esophagus, stomach, colorectal, kidney, thyroid, brain, sarcomas, female genitals	Breast, lung, stomach
Testis cancer	Lung, esophagus, stomach, pancreas, colorectal, kidney, bladder, sarcomas	Stomach
Breast cancer	Contralateral breast, lung, esophagus, sarcomas	Contralateral breast
Cervix cancer	Bladder, kidney, rectum, endometrium, ovary	Rectum, bladder, genitals
Prostate cancer	Colorectal, bladder, sarcomas	

2. There is a correlation between RT dose and secondary malignancy probability.

Some clinical associations are well-known from the radiation oncologists who watch survivors from childhood cancer (Table 13.3):

– Hodgkin and breast cancer: the risk of breast cancer is multiplied by 4 after 10 years of follow-up and the rate of breast cancer reaches 30% in women 30 years after treatment. It would appear that the risk is also higher if the irradiation occurs during puberty. Screening is essential in this population.
– Secondary brain tumors after prophylactic or curative whole brain RT for lymphoblastic leukemia and primary brain tumors.
– Osteosarcoma after retinoblastoma, Ewing tumors, and soft tissue sarcoma. The relative risk is respectively 30.5 and 2.4 after these pathologies. Classically, radiation-induced osteosarcomas are more serious than the primary ones.
– In addition to hormonal insufficiency, there is a significant risk of cancerization in the case of the thyroid. The risk is linear between 1 and 10 Gy then increases more slowly after 20 Gy but remains high up to 40 Gy.

Current Management of Late Effects

Primary Prevention

The screening of constitutionally radiosensitive patients by means of IRS diagnostic tests could allow an a priori adaptation of their cancer treatment. It would thus be possible to recommend therapeutic alternatives, or to adapt the dose or volumes treated to the individual status, provided these modifications are validated in non-inferiority clinical trials. Several approaches are proposed [78]: radiation-induced lymphocyte apoptosis [79], quantification of radiation-induced pATM [80], TGFβ1

genetic variation [81], spontaneous transcriptomic signature targeting RNA involved in RT-induced fibrosis. However, there is currently no standard technique recommended for daily practice. Recommendations were recently published by the *American Society for Radiation Oncology* [82].

In order to improve the tolerance profile of RT, we can also raise various physical, technological, and biological approaches.

Hyperfractionation consists of delivering a dose per session lower than 1.8 Gy—eventually more than one session a day. The total dose is higher, but the total duration of treatment does not vary. This hyperfractionation has a protective effect on slowly renewing tissues affected by late toxicities, provided that a period of 4–6 h is observed between the fractions [83].

Reducing the tissue volume irradiated at high doses also reduces the incidence of toxicities. Advanced techniques of external beam RT, brachytherapy, and hadrontherapy meet this objective [84]. Controlling patient and organ movements during or between RT sessions is also moving in this direction through the development of image-guided RT and adaptive RT. Protocols for partial irradiation of organs are being evaluated in order to reduce the tissue volume irradiated at high doses in selected indications, in particular, in breast and bladder cancer [85].

The protective power of selective thiol-containing agents against radiation damage to normal tissues has been known for more than 40 years [86]. Multiple randomized clinical trials have evaluated amifostine for the prevention of xerostomia in patients receiving RT or chemoradiotherapy for head and neck cancer. These trials have given conflicting results, and the role of amifostine in this setting remains uncertain. The routine use of amifostine has been abandoned in most institutions due to severe adverse reactions leading to contra-productive RT protraction.

Secondary Prevention: Treatment of Subclinical Chronic Reactions and Early Diagnosis of Sequels

Early diagnosis of toxicities is possible when subclinical biological or radiological signs appear in relation to unusual early or late toxicity events. Imaging methods are developing in that intent—such as radiomics and functional MRI [87, 88].

Biological biomarkers are also being studied; e.g., TGF-β1 and IL-6 in prediction of radiation lung disease [89].

When an unusual early toxicity occurs, specific supportive care may prevent the onset of generic or even Consequential Late Effects. Corticosteroids, in particular topicals, occupy a prominent place. RT can then be continued, interrupted momentarily or even definitively depending on the severity of the reactions. In the second situation, the total dose can be increased to counter the effects of tumor repopulation.

Tertiary Prevention: Treatment of Symptomatic Sequels

Radiation-induced late complications are generally considered irreversible with a complex pathophysiology involving chronic inflammation, micro vasculopathy, fibrosis, and necrosis. When identified during the long-term follow-up, countermeasures may be proposed to mitigate these reactions. Depending on their severity and impact on survival quality, the current strategies include:

1. anti-inflammatory treatments (steroids or nonsteroids) and angiotensin II receptor antagonists [90]; Steroids at a minimal dose of 1 mg/kg/day for a minimum of 4–6 weeks are recommended.
2. antioxidant treatments such as superoxide dismutase, tocopherol (vitamin E) preferably combined with pentoxifylline [91]. Randomized trials evidenced the benefit of the combination on the prevention or reversion of radiation-induced fibrosis. However, the prophylactic use of pentoxifylline is currently not established as a routine management approach. In therapeutic intent, the recommended posology is pentoxifylline (800 mg/day) plus tocopherol (1000 units/day) for at least 6 months.
3. Bevacizumab has been proposed as a treatment for RN by its anti-edematous action via the reduction in vascular permeability. It helps prevent angiogenesis by inhibiting VEGF and therefore slows the progression of radionecrosis in brain, in particular [92, 93].
4. Invasive conservative surgeries such as dilatation and stent implantation for stenoses (e.g., esophagus, ureter), and surgical treatment of adhesions and strictures—keeping in mind that interventions potentially can worsen the underlying fibrosis, and thereby exacerbating symptoms. Targeting telangiectasia, Argon plasma electrocoagulation consists of monopolar electrocoagulation without contact with the treated mucosa using an inert, colorless, nonflammable, and nontoxic gas [94]. The coagulation obtained is homogeneous on the surface and, in principle, limited in depth (2–3 mm). Several sessions are often necessary with a correlation between the number of sessions required and the extent of the lesions to be treated. Many open studies have reported effectiveness rates of over 80% on bleeding after 1–3 sessions on average. Some complications have been described, in particular, fever with bacteremia, urinary disorders, mucosal ulcerations, hemorrhages from pressure ulcers, rectal strictures, and some colonic perforations attributed to an endoluminal accumulation of colonic gas. In addition, argon plasma electrocoagulation may be ineffective, especially with heavy bleeding that "absorbs" and renders the electric current inoperative. Similarly, certain radiation lesions of the lower rectum, as well as very extensive diffuse congestive proctitis, are other limitations of the technique. Formalin treatment may be an alternative in proctitis. Another therapeutic option, MRI-guided laser thermal ablation was evaluated in a prospective multicenter study including 42 patients with brain radionecrosis or histologically confirmed progression. This treatment carries little risk and seems effective for radionecrosis with 100% local control and more than 80% survival at 6 months.

5. Hypoxia reversion with hyperbaric oxygen (HBO) [95]; The benefit of HBO has been assessed in RT-induced lymphedema in breast cancer and jaw osteoradionecrosis and proctitis. In practice, daily 45–120 min sessions are carried out on an outpatient basis in a hyperbaric chamber. Compression ranges from 2 to 2.5 atmospheres. The total number of sessions is variable because the response time to treatment is random and because there is no consensus on a maximum number of compressions beyond which treatment would be in vain. Clinical cases and open studies with at least 100 patients have reported efficacy rates of over 75% on bleeding after an average of 24–67 sessions.
6. In addition to the difficulties of its implementation in practice, complications have been reported, especially, such as barotraumatic otitis, chest pain, or visual disturbances, most often transient. In fact, a preliminary examination of the eardrums is necessary and certain contraindications (claustrophobia, cardiac conduction disorders, poorly controlled epilepsy, bronchopathy, pneumothorax, etc.) must be observed.
7. Cell therapy has recently been shown to be effective in the context of severe accidental irradiation, consisting of injecting autologous mesenchymal stem cells in situ [96].

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Evidence-Based Screening for Recurrence

14

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Abbreviations

CT	Computed tomography
LVI	Lymphovascular invasion
MRI	Magnetic resonance imaging
NED	No evidence of disease
US	Ultrasound

Breast Cancer

In this chapter, the surveillance for breast cancer recurrence will refer to the follow-up of breast cancer patients with No Evidence of Disease (NED) after completion of primary therapy including surgery, chemotherapy, and radiotherapy.

No randomized trial so far can confirm a specific protocol of follow-up [1]. Based on ESMO, ASCO, and NCCN recommendations, the elements of surveillance include regular history and physical examination as well as mammography [2–4]. The purpose of history and physical examination is to reveal possible symptoms and signs of local and systematic recurrence but the evidence on the optimal frequency is inconclusive [1]. Mammographic surveillance is intended to detect both local recurrence and contralateral breast cancer. Annual mammography is the standard of care but the evidence on the optimal scheduling is also insufficient [5]. MRI has not been proven superior so far as compared to mammography [6] but it may be considered in patients with genetic predisposition.

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Table 14.1 Breast cancer surveillance strategy

Recommended	Assessment
Patient education (symptoms and signs)	Lumps, nipple discharge, changes of breast skin and surgical incision, weight loss, anorexia, fatigue, bone pain, cough, chest pain, dyspnea, abdominal pain, headache, vomiting, jaundice, abdominal distention, muscular strength, sensory and gait abnormalities, speech, vision and memory disturbances, and confusion
History and physical examination	Every 3–4 months in the first 2 years (every 6 months for low risk and DCIS), every 6–8 months for years 3–5, and then annually
Mammography	Annually
Not routinely recommended	
CBC, LFTs, ALP, tumor markers (CA-15.3), CT scan	As clinically indicated

In the absence of symptoms, there is no survival advantage to incorporate laboratory and imaging studies compared with simple clinical follow-up, as revealed by two randomized trials [7, 8] and a meta-analysis [9]. However, these are studies conducted in an era of outdated diagnostic and therapeutic modalities that may confound this evidence [10]. New trials are needed to evaluate subsets of patients with specific recurrence patterns and molecular subtypes.

An indicative follow-up strategy is in Table 14.1.

Colorectal Cancer

Posttreatment surveillance in colorectal cancer is intended to identify potentially resectable disease recurrence with the aim to improve survival. Although it remains debatable, intensive surveillance seems to favor survival as compared to less intensive follow-up. The evidence has been obtained from patients with stage II and III disease, whereas there are only limited data from patients with stage I and resected stage IV disease with no evidence of disease (NED).

Results from randomized controlled trials are conflicting. Several meta-analyses have shown improved survival in patients who underwent intensive surveillance [11–14]. However, the most recent update of a Cochrane meta-analysis failed to demonstrate survival benefit in the intensive follow-up group despite having received more salvage operations with curative intent [15]. This discordance could be attributed to the large heterogeneity regarding the surveillance strategies applied in different trials [16], with differences in the elements, duration, frequency, and population of the follow-up.

In line with the ESMO [17], ASCO [18], and NCCN [19] guidelines, an intensive protocol of surveillance is recommended. History and physical examination, periodic CT scanning, CEA measurement, and colonoscopy are the approved elements of surveillance. The optimal surveillance strategy is debatable and the suggested protocols are based on expert panel consensus. Complete blood count, liver function

Table 14.2 Colorectal cancer surveillance strategy

Recommended	Assessment
History and physical examination and CEA	Every 3–6 months the first 3 years and every 6–12 months at years 4 and 5
CT abdomen, pelvis, chest	Every 6–12 months the first 3 years for patients with higher risk of relapse (e.g., stage III, high-risk stage II) and then as clinically indicated until year 5
Endoscopy	One year after surgery and every 3–5 years thereafter
Not recommended	
CBC, LFTs PET/CT, Ro chest, FOB	As clinically indicated

tests, fecal occult blood testing, chest radiography, and PET/CT are not endorsed elements by any expert panel.

An indicative follow-up strategy is in Table 14.2.

Gastric Cancer

Gastric cancer recurrence after curative resection can be categorized as locoregional (either at the resection site or within the lymph nodes), peritoneal, or hematogenous.

Recurrent gastric cancer is not usually amenable to surgical resection due to the aggressive nature of the disease. Palliative chemotherapy offers survival benefit as compared to best supportive care [20] but there are no randomized trials assessing whether an intensive surveillance with endoscopy, imaging, and laboratory studies performs better compared to a clinical follow-up.

Data derived from retrospective studies indicate that intensive strategies may result in earlier detection of recurrence but without improving overall survival [21–23]. Considering the lack of strong evidence, the components, frequency, and duration of follow-up are currently based on experts' consensus [24].

The ESMO guidelines suggest that the follow-up should be adapted to the individual patient and stage of the disease [25]. The NCCN suggests a specific protocol which stratifies patients according to the risk of recurrence [26].

Considering the most recent recommendations, we propose the following surveillance protocol in Table 14.3 in line with the NCCN.

Lung Cancer

Surveillance after lung cancer therapy with curative intent may lead to the early detection of an asymptomatic relapse and of a second primary.

In NSCLC, data from retrospective studies suggest a surveillance strategy which includes regular clinical examination and CT scans [27, 28]. The randomized NLST trial demonstrated a decrease in mortality when high-risk patients without a

Table 14.3 Gastric cancer surveillance strategy

Recommended investigation	Tis (ER)	Stage I	Stages II and III
History and physical examination	Every 3–6 months the first 2 years, every 6–12 months for years 3–5, and annually thereafter	Every 3–6 months the first 2 years, every 6–12 months for years 3–5, and annually thereafter	Every 3–6 months the first 2 years, every 6–12 months for years 3–5, and annually thereafter
CT abdomen, pelvis, chest	As clinically indicated	As clinically indicated	Every 6–12 months the first 2 years and then annually until year 5
Endoscopy	Every 6 months the first year and then annually for 3 years	**T1a (ER)**: Every 6 months the first year and then annually for 5 years **T1a and T1b (surgery)**: as clinically indicated	As clinically indicated if treated with partial or subtotal gastrectomy No role in total gastrectomy (unless symptomatic)
CBC and biochemistry	As clinically indicated	As clinically indicated	As clinically indicated

ER endoscopically resected; *Tis* T in situ

previous history of lung cancer were screened with low-dose CT compared to simple X-ray. However, that was a study examining a screening method instead of a surveillance strategy [29]. A meta-analysis of heterogeneous trials has shown that intensive follow-up with regular imaging was associated with a nonsignificant trend towards improved survival [30]. However, preliminary results from the IFCT-0302 trial did not find any difference in the OS between a surveillance strategy consisting of clinical examination and CT compared to clinical examination and chest X-ray. Considering a trend towards better survival in the CT arm, the authors commented that longer follow-up may reveal a benefit [31]. Regarding FDG-PET/CT, it did not perform better at detecting disease recurrence compared to standard radiologic examinations in a prospective study [32].

The ESMO, ASCO, and NCCN guidelines recommend a follow-up with history and physical examination plus CT chest every 6 months for the first 2 years with the aim to detect disease recurrence and annually thereafter with a focus to reveal a second primary [33–35].

There is a lack of evidence on surveillance after definitive treatment for SCLC. The experts' panels suggest a frequent follow-up due to the high risk of recurrence [35]. Although most relapses are incurable, an intensive follow-up may detect asymptomatic recurrences while patients are in good PS [36, 37]. Furthermore, patients having been treated for SCLC are also at high risk for developing a second primary [38].

Regarding the use of brain MRI as part of the surveillance strategy, there is a lack of evidence from randomized trials for both NSCLC and SCLC [35]. Indirect evidence suggests that brain MRI is of value for the follow-up of SCLC patients [35]. Given the high incidence of brain metastases in SCLC and considering that

Table 14.4 Lung cancer surveillance strategy

Recommended	NSCLC (stages I, II, III)	SCLC (stages I, II, III)
History and Physical examination	Every 6 months for the first 2 years and annually thereafter	Every 3 months for the first year. Every 3–6 months for the second year with lengthening of the interval thereafter
Imaging	CT chest including adrenals every 6 months for the first 2 years and low-dose CT chest annually thereafter	CT scan every 3–6 months for the first 2 years with lengthening of the interval thereafter. Annual low-dose CT chest after 5 years. MRI brain every 3 months for the first year, every 6 months for the second year. As clinically indicated thereafter
Not recommended		
Circulating biomarkers, FDG-PET/CT		

prophylactic cranial irradiation (PCI) increases the OS in patients with SCLC in complete remission [39], brain MRI may lead to early detection of asymptomatic brain lesions and treatment before the development of debilitating neurological symptoms with potential benefit in the quality of life. There is currently no recommendation for brain MRI in the follow-up of NSCLC patients [35].

In line with the most recent ASCO guidelines and considering the ESMO and NCCN recommendations on lung cancer surveillance [35], we recommend the following protocol in Table 14.4.

Testicular Germ Cell Cancer

Although the cure rates of testicular cancer are high, there is always a risk of relapse [40]. Recurrent testicular cancer can be curable thus justifying the need for surveillance.

Surveillance after treatment with curative intent is tailored to the histology, stage, type of therapy, and treatment success [41]. There is a lack of evidence from randomized studies on the optimal follow-up. The elements of follow-up include history and physical examination, tumor markers, and radiologic examinations [41–44]. Currently, there is a tendency to reduce the frequency of CT scans due to concerns about potential radiation-induced malignancy [45].

With reference to the ESMO guidelines, patients can be stratified in the three following surveillance plans [41].

Patients with seminoma stage I (on active surveillance or after adjuvant carboplatin or radiotherapy). Most relapses occur within the first 2 years and mainly concern the para-aortic nodes [46]. Abdominal CT or MRI are the recommended radiologic studies. The rate of thoracic recurrence is low and there is no role for chest X-ray or CT chest unless clinically indicated [47]. Although the tumor markers only rarely increase in seminoma relapse without radiologic evidence [48],

at the moment they are recommended by ESMO [41], considered optional by NCCN [43], whereas the ASCO panel has recommended against its use in the surveillance of patients with stage I seminoma [49].

Patients with non-seminoma stage I on active surveillance. The majority of relapses also occur within the first 2 years and most of them within a year post orchiectomy [40, 50]. Patients with high-risk non-seminoma with lymphovascular invasion (LVI) have a risk of relapse of around 50% without adjuvant chemotherapy, while patients without LVI have a risk of relapse of around 15% [40, 51]. In retrospective studies, 50% of patients had only retroperitoneal relapse [44] and 19% had thoracic recurrence with evidence of disease on the chest x-ray [52]. The latter allows elimination of the CT chest from the surveillance plan [52]. The recommended components of the surveillance plan by the ESMO and NCCN are history and physical examination, tumor markers, and abdominal CT or MRI [41, 43]. The frequency of the CT scans can be safely reduced to two scans in the first year post orchiectomy, based on the results of the MRC TE08 randomized trial [53].

Patients after adjuvant treatment or complete remission for advanced disease. In this category, the ESMO includes all patients who have either received adjuvant treatment or curative chemotherapy for good and intermediate prognosis metastatic testicular cancer according to the classification of International Germ Cell Cancer Collaborative Group (IGCCCG) and have achieved complete remission [41]. There is no high-quality evidence and the recommendations stem from expert consensus.

Patients who had not a complete remission or had a disease of poor prognosis should be provided with an individualized surveillance plan [41].

The follow-up beyond 5 years mainly aims to the detection of therapy-related toxicities, as a very late relapse is a rare occurrence [54].

In accordance with the ESMO guidelines, we suggest the following surveillance plan in Table 14.5 [43].

As stated by the most recent ESMO guidelines, follow-up beyond 5 years is according to the survivorship care plan.

An individualized follow-up is recommended for poor prognosis patients.

Epithelial Ovarian Carcinoma

The majority of patients with epithelial ovarian carcinoma post primary treatment will eventually relapse. However, the evidence on whether early asymptomatic relapse can lead to improved clinical outcome is inconclusive [55, 56].

The only available randomized controlled trial published, the MRC OV05/EORTC 55955 collaborative trial demonstrated that the early administration of chemotherapy on the basis of a rising CA125 did not increase survival as compared to patients that received chemotherapy on symptomatic recurrence [57]. However, this trial did not examine the potential added benefit of a secondary cytoreduction in surgically amenable relapses [58]. Moreover, this trial was conducted before the emergence of maintenance treatment with parp inhibitors [59]. New randomized controlled trials are needed [55].

Table 14.5 Testicular germ cell cancer surveillance strategy

Recommended investigation	Seminoma stage I on active surveillance or after adjuvant carboplatin or radiotherapy	Non-seminoma stage I on active surveillance	Advanced disease after adjuvant treatment or complete remission (good and intermediate prognosis)
History and physical examination and tumor markers	Twice on years 1, 2, and 3, once on years 4 and 5	4 times on years 1 and 2, twice on year 3, 1–2 times on years 4 and 5	4 times on years 1 and 2, twice on years 3, 4, and 5
Chest X-ray	Not recommended	Twice on years 1 and 2, once on year 3 if LVI+, at 60 months if LVI+	1–2 times on year 1, once on years 2, 3, 4, and 5
CT/MRI abdomen and pelvis and retroperitoneum	Twice on years 1 and 2, at 36 and 60 months	Twice on year 1, at 24 months and optionally at 36 and 60 months	1–2 times on year 1, at 24 months and optionally at 36 and 60 months
CT chest	Not recommended	Not recommended	As per CT abdomen in case of pulmonary metastasis at diagnosis

LVI lymphovascular invasion

Table 14.6 Epithelial ovarian carcinoma surveillance strategy

Recommended	Assessment
Patient education	**Alarming symptoms** Weight loss, bloating, pain (mainly abdominal or pelvic), abdominal distention, leg swelling, appetite loss, nausea, vomiting, constipation, not passing gas, urinary retention, dyspnea, cough
History and physical examination and CA125	Every 3–4 months the first 2 years, every 6 months during years 3–5[a]. Beyond 5 years should be individually discussed
Not recommended	
US, CT scan, PET/CT, MRI, chest X-ray	As clinically indicated

[a]As stated in the recent ESMO-ESGO guidelines, the plan should be individualized according to prognostic factors and treatment modalities

For the moment, the CA125 is considered an important element in monitoring ovarian cancer recurrence as suggested by the ESMO-ESGO and NCCN committees [59, 60]. Other important components include the patient education for alarming symptoms as well as the history and physical examination [59]. Routine imaging is not recommended unless indicated by a rising CA125 or clinical criteria [59–61].

In line with the ESMO-ESGO consensus conference recommendations on ovarian cancer [59], we suggest the following surveillance plan in Table 14.6.

Endometrial Cancer

The majority of recurrences occur within 3 years posttreatment. The recurrence rate spans from 2 to 15% for early stages and can extend to 50% for advanced stages [62]. Around 70% of the relapses are symptomatic [63]. There are no prospective studies to assess different surveillance strategies. The evidence stems from retrospective studies.

It is controversial whether patients with asymptomatic relapse detected on follow-up visits have better outcome compared to symptomatic patients [64–67]. A review of symptoms combined with clinical examination can detect the majority of recurrences [68, 69]. Patient education for the alarming symptom is thus a critical element of the surveillance strategy [62, 70].

Although commonly used, the test-pap may not provide additional benefit to detect local recurrence on the vaginal cuff as compared to a thorough clinical examination combined with symptomatology [71, 72]. CA125 investigation should be individualized in cases with advanced disease, serous histology, or increased pretreatment levels as suggested by the Society of Gynecologic Oncology (SGO) [62]. Furthermore, radiologic imaging with CT scans, pelvic ultrasound, and PET/CT should be reserved in cases with clinically suspected relapse [62, 63, 73].

Considering the SGO recommendations on posttreatment surveillance on gynecologic malignancies [62] and in line with the ESMO guidelines on endometrial cancer [73], we suggest the following surveillance plan in Table 14.7.

Prostate Cancer

In this chapter, posttreatment surveillance will refer to the follow-up of patients with prostate cancer after local treatment with curative intent that include either radical prostatectomy or external beam radiation therapy or

Table 14.7 Endometrial cancer surveillance strategy

Recommended	Assessment
Patient education	**Alarming symptoms** Vaginal or rectal bleeding, hematuria, weight loss, bloating, pain (abdominal, pelvic, hip, back), abdominal distention, leg swelling, appetite loss, nausea, vomiting, constipation, not passing gas, urinary retention, dyspnea, cough
History and physical examination (including speculum, pelvic and rectovaginal examination)	**Low risk**. Every 6 months the first year, every 6–12 months the second year, once a year thereafter. **High risk**[a]. Every 3 months the first 2 years, every 6 months during years 3–5, and once a year thereafter
Not recommended	
Pelvic US, CT scan, PET/CT, chest x-ray, MRI, CA125, pap-test	As clinically indicated

[a]As stated by SGO, high risk is defined as an advanced stage or high-risk histology

Table 14.8 Prostate cancer surveillance strategy

Recommended	Assessment
PSA measurement and Disease-specific history and DRE (if considered)	At 3, 6, and 12 months the first year, then every 6 months for 3 years, and annually thereafter
Not recommended	
TRUS, Bone scintigraphy, CT, PET/CT, MRI	As clinically indicated

brachytherapy. The majority of recurrences occur within 5 years and the estimated risk is around 30% [74].

Prostate-Specific Antigen (PSA) monitoring is considered the cornerstone of the follow-up [75]. The definition of PSA recurrence is determined by the prior definitive treatment. In reference to post-radical prostatectomy, the relapse is defined by a constitutively rising PSA [75, 76], whereas post-radiotherapy is defined as an increase of 2 ng/ml above the posttreatment PSA nadir [75, 77].

The role of history, physical examination, and Digital Rectal Examination (DRE) is debatable, since the majority of recurrences are asymptomatic and abnormal DREs are almost always associated with a PSA rise [78, 79]. However, patients may progress without a simultaneous increase of PSA in a small percentage of cases with undifferentiated histology [80]. According to the recommendations of the European Association of Urology (EAU), PSA monitoring combined with disease-specific history are the recommended elements of follow-up and DRE can also be considered [75]. The ESMO panel does not recommend routine DRE for asymptomatic patients when the PSA is controlled [81], whereas the NCCN suggests annual DRE for the rare cases of local recurrence without elevation of PSA and for potential detection of colorectal cancer [82].

Since PSA elevation almost always precedes clinical recurrence, imaging studies with transrectal ultrasound (TRUS), bone scintigraphy, CT scans, MRI, PET/CT are not indicated for routine use unless in the presence of symptoms or in cases where the radiologic findings affect the treatment decision [75].

In line with the recommendations of the EAU [75], we suggest the following surveillance plan in Table 14.8.

Renal Cell Carcinoma

In this section, posttreatment surveillance will refer to the follow-up of patients after primary treatment for localized disease either surgical (radical or partial nephrectomy) or ablative.

The majority of recurrences occur within 3 years post nephrectomy [83] and around 30% of patients will eventually develop relapse [84, 85]. Late recurrence is rare but certain patients, especially the low-risk, can experience relapse beyond 5 years [84, 86]. The site of recurrence can either be locoregional or distant. The most common metastatic site is the lungs, followed by the bones, the liver, and the brain [87].

Table 14.9 Renal cell carcinoma surveillance strategy

Recommended	Low risk	High risk
History and physical examination	Every 3–6 months the first 3 years and then annually until year 5	Every 3–6 months the first 3 years and then annually until year 5
CT abdomen and chest	Annually until year 5	Every 3–6 months the first 3 years and then annually until year 5

Follow-up beyond 5 years as clinically indicated

Patients who have relapse detected on follow-up may have a better prognosis as compared to those who have symptomatic recurrence [88, 89]. However, it is uncertain whether a particular follow-up strategy is associated with better clinical outcome.

Since the risk of recurrence and death is dependent on patient and tumor characteristics [86, 90], the experts' panels recommend risk-stratified surveillance plans. The NCCN [84] and the American Urologic Association (AUA) [91] stratify patients based on the stage after surgical treatment, whereas the ESMO [92] and the European Association of Urology (EAU) [89] distinguish patients in low-and high-risk groups based on scoring models such as the stage, size, grade, and necrosis (SSIGN) or the University of California Los Angeles Integrated Staging System (UISS).

An indicative follow-up plan after nephrectomy is in Table 14.9.

Bladder Cancer

At diagnosis, 75% of patients have non-muscle-invasive Bladder Cancer (NMIBC), while the rest present with muscle-invasive Bladder Cancer (MIBC).

According to the European Association of Urology (EAU), NMIBC patients are stratified into three groups depending on the risk of recurrence [93]. These are the low-risk [primary, solitary, TaG1,[1] < 3 cm, no carcinoma in situ (cis) tumors], the intermediate [not defined in the low- and high-risk category tumors], and the high-risk groups [either T1 or G3* or CIS or multiple, recurrent, and large (>3 cm) TaG1G2 tumors (all features present)].

Regarding MIBC, the site of recurrence can be either local (pelvic), distant, or urothelial [94]. Most local recurrences occur during the first 2 years after radical cystectomy (RC) affecting the surgical site or the Lymph Nodes (LNs) of 5–15% of patients. Risk factors are advanced pathologic stage, LN involvement, positive surgical margins, the extent of LN dissection, and peri-operative chemotherapy [95]. Distant recurrences are manifested in approximately 50% of patients during the first 3 years post RC affecting the LNs, the lung, the liver, and bones. Predictors of distant recurrence are the pathologic stage and the LN involvement [95]. Urothelial recurrence can develop either in the urethra or the upper urinary tract (UTUC). The latter is the most frequent site of late relapse. Predictors of urethral recurrence are

[1] G1, G2, G3: Grade 1, Grade 2, Grade 3 tumors respectively.

Table 14.10 Bladder cancer surveillance strategy

Recommended investigation	NMIBC	MIBC post RC	MIBC post TMT[a]
Imaging	Annual CTU[b] for high-risk tumors	CT abdomen and chest every 6 months the first 3 years and then annually until year 5. CTU[b] is considered when risk factors of UTUC are present	CT abdomen and chest every 6 months the first 3 years and then annually until year 5
Urinary cytology and cytoscopy	At 3 months after TURB[c] **Low-risk**: Then at 12 months and annually thereafter. Discontinuation can be considered after 5 years **High-risk**: Every 3 months for 2 years, then every 6 months until year 5, and annually thereafter **Intermediate risk:** individualization between low-/high-risk	In cases of multifocality, CIS and tumor in prostatic urethra	Every 3–6 months the first 3 years. Then every 6 months

[a]*TMT* = trimodality treatment
[b]*CTU* = CT urography
[c]*TURB* = transurethral resection of bladder

cystectomy for NMIBC, history of recurrent NMIBC, type of bladder substitution, and prostate involvement, while multifocal disease, NMIBC with CIS or positive ureteral margins after RC are risk factors for UTUC [95].

Although the evidence on posttreatment follow-up is of low-level as it stems only from retrospective studies, reasonable suggestions can be proposed on surveillance for both NMIBC and MIBC based on the risk and the site of recurrence [96].

In line with the EAU-ESMO consensus statements, we recommend the following surveillance plan in Table 14.10 [93, 94].

Head and Neck Cancers

Patients with head and neck cancers after definitive treatment should be followed with the aim to detect either recurrence or a second primary as well as posttreatment complications.

Although early detection of local recurrence can lead to salvage treatment, it is uncertain whether posttreatment surveillance offers survival benefit [97–100].

The length of follow-up is generally 5 years, but in certain high-risk patients may last for longer [101]. Most recurrences occur during the first 2 years hence the frequency is higher during this period [101].

Table 14.11 Head and Neck cancers surveillance strategy

Recommended	Assessment
Patient education	**Alarming symptoms and signs** Pain, weight loss, dysphagia, hoarseness, dyspnea, bleeding, lumps, cranial nerve deficits
History and physical and mirror examination and fiberoptic endoscopy	Every 1–3 months the first year, every 2–6 months the second year, every 4–8 months the years 3–5, and annually thereafter
Imaging	CT or MRI within 3–4 months or FDG-PET/CT (after RT or chemo/RT) within 3–6 months. Then as clinically indicated or tailored to specific patient and tumor characteristics. Consider annual low-dose CT chest for screening for second primary in the lung

Regarding the elements of follow-up, patient education is of great importance since most recurrences can manifest with symptoms and signs that can be monitored by the patient [101, 102]. A complete and thorough physical examination of the head and neck combined with fiberoptic nasopharyngolaryngoscopy is recommended [101, 102]. CT, MRI, and FDG-PET/CT are the indicated imaging modalities for surveillance [103]. The intensity of imaging is not well defined [100]. In a retrospective analysis, patients with a negative PET/CT imaging at 3 months post-therapy had similar survival with patients that received additional scans at 12 and 24 months [104]. An individualized approach tailored to patients' and tumors' characteristics may be reasonable [105].

There are no prospective studies to assess different follow-up protocols. Recommendations are provided by the scientific societies of the NCCN [106] and ESMO [107]. However, the ESMO does not specify a time schedule.

We suggest the following surveillance protocol in Table 14.11.

Sarcoma

Sarcomas are rare neoplasms; therefore, high-quality evidence lacks due to scarcity of studies.

The recurrence after primary treatment can be either local or metastatic. The most common metastatic site is the lungs. Depending on the location and histology of the primary tumor, other sites such as the liver (e.g., retroperitoneal sarcoma, GIST), skeleton (e.g., myxoid liposarcoma), peritoneum, or retroperitoneum may be involved. The histology, grade, size, depth, completeness of resection, and age are risk factors for soft tissue sarcoma (STS) recurrence [108].

Posttreatment surveillance is reasonable. Salvage treatment of local relapse is feasible in certain cases [109] and metastasectomy in patients with limited number of lung lesions may be curative [110]. In a prospective randomized trial, a follow-up strategy of higher frequency and more intensive imaging did not demonstrate additional benefit [111]. Furthermore, an intensive follow-up is not cost-effective [112]. Local recurrences are often reported by patients; hence, patient education should be encouraged [113]. Elements of the follow-up are the history and physical examination, imaging of the primary site, and chest X-ray or CT chest [113, 114].

Table 14.12 Sarcoma surveillance strategy

Recommended investigation	Soft tissue sarcoma	Bone sarcoma
History and physical examination	**Intermediate /high-risk patients** Every 3–4 months the first 2–3 years, then twice a year up to year 5 and once a year thereafter **Low-risk** Every 4–6 months the first 3–5 years, then annually	**High-grade tumors** Every 3 months the first 2 years, every 6 months for years 3–5, every 6–12 months for years 5–10, and every 0.5–2 years thereafter **Low-grade tumors** Every 6 months the first 2 years and then annually
Imaging	US or MRI in case of clinical suspicion or clinically inaccessible primary site. Chest X-ray during the same intervals (or CT chest on clinical suspicion)	Local imaging with X-ray, CT, or MRI and chest X-ray or low-dose CT chest, as clinically indicated

Recommendations suitable for all circumstances would be an unreliable endeavor due to the large heterogeneity of sarcomas. The ESMO stratifies patients on the basis of the risk of recurrence for soft tissue sarcomas (STS) [115] and the tumor grade for bone sarcomas (BS) [116], whereas the NCCN provides separate surveillance plans depending on the location and histology for STS [117] and BS [118].

In line with the ESMO guidelines, we suggest the following surveillance protocol in Table 14.12.

Cutaneous Melanoma

Surveillance for patients with cutaneous melanoma who have NED after primary treatment, aims to detection of either a relapse (locoregional or distant) or a new primary skin tumor.

It is assumed that early detection of relapse can lead to curative treatment and systemic recurrence with low-disease burden may be associated with better response to immunotherapy or targeted therapies. However, there are no studies to prove this assumption.

As the stage increases, the risk of recurrence and the likelihood of distant metastasis increases. Patients with advanced stages tend to manifest relapse earlier but the risk decreases over time [119–121].

Recurrences are frequently reported by patients [122], therefore patient education for symptoms and signs and targeted clinical examination are valuable practices of the follow-up. Several analyses from prospective databases have shown that only a minority of relapses were detected by imaging modalities [123, 124]. There is a lack of evidence on whether imaging improves survival [125]. However, the advances in melanoma management mandate new prospective studies to evaluate the role of imaging-intensified follow-up.

In a meta-analysis, ultrasound, CT, PET, and PET/CT were assessed for their utility on staging and surveillance in melanoma patients. Ultrasound and PET/CT were found to be superior for detecting lymph node and distant metastases, respectively [126].

The NCCN panel provides stage-specific recommendations and acknowledges that incorporation of imaging can be considered at physician's discretion [127]. The ESMO acknowledges the lack of consensus. According to the panel, the follow-up interval can vary and imaging can be performed in high-risk patients [128].

We suggest the following surveillance protocol in Table 14.13.

Pancreatic Adenocarcinoma

Surveillance after curative treatment for pancreatic carcinoma is intended to facilitate supportive care and detection of recurrence.

In a retrospective analysis, half of the recurrences were detected prior to symptom presentation in patients who went through a regular clinical and radiological follow-up. Furthermore, patients that had symptomatic recurrence had shorter survival [129]. In another retrospective analysis from Surveillance, Epidemiology, and End Results (SEER)-Medicare database, there was no survival benefit in patients who underwent annual routine CT scans. Furthermore, it was found that increased frequency and intensity of follow-up protocols were associated with increased cost without survival benefit in cost-effectiveness analysis [130].

The ESMO panel states that there is no evidence that surveillance after primary treatment offers survival benefit and the follow-up should be concentrated on supportive care [131]. The NCCN states that earlier detection of recurrence may facilitate participation in investigational studies and proposes a specific follow-up protocol [132]. The ASCO suggests that patients should be monitored for treatment-related toxicities and relapse but acknowledges that the frequency, duration, and elements of follow-up are not defined [133].

We propose a surveillance plan that considers supportive issues, psychosocial factors, and patient expectations in Table 14.14.

Table 14.13 Cutaneous melanoma surveillance strategy

Recommended investigation	Assessment
History and physical examination	Every 3 months the first 3 years and every 6–12 months thereafter (When the risk of recurrence is low, the frequency can decrease)
Imaging	US, CT, PET/CT as clinically indicated (e.g., risk of relapse, clinical suspicion)

Table 14.14 Pancreatic adenocarcinoma surveillance strategy

Recommended investigation	Assessment
History and physical examination	Every 3–6 months the first 2 years and every 6–12 months thereafter
CT scans (abdomen and chest)	As clinically indicated
CA 19–9	As clinically indicated

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Survivorship Follow-Up: Update About Evidence-Based Screening for Secondary Cancers

15

Charlotte Demoor-Goldschmidt and Florent de Vathaire

Rationale

Cancer societies have reported a decline in the death rate from cancer over the past two decades due to progress in prevention, diagnosis, and treatment. Nevertheless, cancer remains a deadly disease that justifies aggressive therapeutics. This has led to a greater concern about potential long-term sequelae, of which, in particular, secondary cancers occurring within a few years to more than 40 years after diagnosis of first cancer. The mortality associated with second primary cancers is important, as more than one-half of patients with two incident cancers died of their secondary malignancy [1–3]. Nevertheless, the benefits of therapy outweighed any risks of second neoplasms. The situation of patients with multiple metachronous primaries is of increasing relevance and importance, as second cancers constitute 15–20% of all cancer diagnoses in the cancer registries and concern about 1 in 6–10 patients diagnosed with cancer [2, 4–6]. Several definitions exist to define these cancers occurring over time. The Surveillance Epidemiology and End Results (SEER) database recommends to use an interval of 2 months between the two cancers to qualify the second one as "metachronous" [7], while the International Agency for Research on Cancer (IARC) suggests an interval of more than 6 months [8]. Moreover, it is usual to distinguish "second cancers" from the "secondary

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cancers" with a share of iatrogenicity because of being related to the treatments received [9, 10]. These secondary cancers seem to be a small part of second cancers in registries but just one study analyzed precisely the proportion of radiotherapy (RT)-related cancers [2]. With a median follow-up of 12 years, just 8% of second cancers were classified as probably secondary to radiotherapy. This proportion can increase with a longer follow-up, when adding other factors, such as chemotherapy/hormonotherapy, or in a specific population, such as children and young adult cancer survivors, among which about 90% of the second cancers occurring in the 40 years following treatment are attributable to radiotherapy (e.g., the Childhood Cancer Survivor Study (CCSS), British Childhood Cancer Survivor Study (BCCSS), collaborative cohort from the Nordic countries cancer registries, Dutch Childhood Oncology Group-Long-Term Effects After Childhood Cancer (DCOG-LATER), and French Childhood Cancer Survivor Study (FCCSS)) or Hodgkin lymphoma survivors, among which it is about 50–60%, and testicular cancer survivors, among which it is about 25% [2, 11–19]. These groups have shown that an increase in second cancer risk persists with advancing attained age. Several factors can explain the bigger impact of treatments among children compared to that for adults—a higher sensitivity to ionizing treatments, a higher rate of genetic susceptibility, a longer life expectancy, and just simply because of the higher impact of a radiation field due to a difference in body size. Second cancers are increasingly relevant considerations for both patients and clinicians and have been often studied in childhood cancer survivors but caution must be taken, as most of them did not take into account the environmental exposures and lifestyle during their adulthood. Cancer survivors initially treated with RT as an adult have a second cancer risk of 1.1–3 times higher than the general population [2]. This risk rises to 5–10 times after childhood cancers [20–23]. Chemotherapy is also known as a risk factor not only for therapy-related acute myeloid leukemia (t-AML) and therapy-related myelodysplastic syndrome (t-MDS) but also for solid tumors, particularly alkylating agents, platinum agents, and anthracyclines [24–30]. The term "treatment-related AML" is often used interchangeably with "secondary AML" when previous chemotherapy is considered to have contributed to its etiology. Moreover, the risk factors from treatment and unknown host factors may confound the calculated risk estimates.

In this chapter, we focus on secondary cancers and review current knowledge about the risk factors and existing recommendations for screening.

Chemotherapy

An analysis of second cancers was done in the Childhood Cancer Survivor Study (CCSS) cohort of survivors diagnosed with cancer before the age of 21 years old between 1970 and 1999 (with a median age at diagnosis of 7.0 years) treated with chemotherapy only ($n = 7448$), chemotherapy plus radiation ($n = 10{,}485$), radiation only ($n = 2063$), or neither ($n = 2158$) [24]. With a median age at last follow-up of 31.8 years, 1498 cancers (excluding cutaneous cancer) were diagnosed among 1344 survivors, of which 229 occurred among 206 survivors treated with chemotherapy

only. The cumulative incidence at 30 years was 3.9% after chemotherapy versus 9.0% after chemotherapy plus radiotherapy, 10.8% after radiotherapy, and 3.4% in neither treatment groups. This led to a 2.8-fold (95% CI [2.5–3.2] increase in the risk of developing second cancer compared with that in the general population. The standardized incidence ratios (SIRs) were for leukemia/lymphoma 1.9 (95% CI, [1.3–2.7]), breast cancer 4.6 (95% CI [3.5–6.0]), soft-tissue sarcoma 3.4 (95% CI [1.9–5.7], thyroid cancer 3.8 (95% CI [2.7–5.1], and melanoma 2.3 (95% CI [1.5–3.5]).

After chemotherapy, the most well-established association between alkylating agents, topoisomerase inhibitors, and platinum agents and second neoplasms concern t-AML and t-MDS, with a dose-dependent risk particularly for alkylating agents. This concerns both childhood and adult cancer survivors (except those with colon cancer) [3, 31, 32]. In the SEER records linked with Medicare in the US including 1619 patients with t-MDS/t-AML, with a mean age of 64.3 years and a standard deviation of 12.2, 1270 patients (78.4%) died, and the median overall survival was 7 months [3]. The poor prognosis can be partly explained by a predominance of unfavorable karyotypes in t-AML, a lower performance status, and a high level of comorbidity [32–35]. The risk is mainly during the first years after exposition and typically declines after 10 years, and the prognosis is often poor compared to that of de novo leukemia [3, 36]. We often distinguish t-AML arising [37]:

- after alkylating agent exposition, which is frequently preceded by t-MDS, with frequently a M1 or M2 type from the French-American-British (FAB) classification, arising typically after a latency of 5–8 years, and often has a complex karyotype with monosomy or partial deletion of chromosome 5/7 [38]. Melphalan or mechlorethamine has been found to impart greater risk than cyclophosphamide [39]. The risk increases with the cumulative dose but not with the schedule of administration. Host characteristics are important and may change the risk, as it has been reported in patients with neurofibromatosis 1 (NF1) or Fanconi syndrome [38].
- after topoisomerase II inhibitor exposition (mainly epipodophyllotoxins and after anthracyclines) [40], concerning mainly AML4 and AML5 of the FAB classification, and rarely preceded by t-MDS, arising typically after a latency under 3 years, and frequently characterized by 11q23 rearrangements involving the MLL gene [11]. The risk increases with the cumulative dose of anthracyclines but data are inconsistent with epipodophyllotoxins. The risk seems to vary with the schedule of administration and prolonged administration of low doses seems to be at lower risk than a weekly or twice-weekly schedule [37].

More rarely, other treatments have been linked with t-AML, such as platinum compounds [3, 41–43], dexrazoxane, azathioprine, G-CSF, radiotherapy [40], and temozolomide [44–49].

Chemotherapy can also increase the risk of a new solid tumor but generally after a latency of more than 10 years, including lung, gastrointestinal, bladder, thyroid, melanoma, and breast cancers, as well as sarcomas. In the CCSS, an association

between solid cancers and chemotherapy was found for dose >750 mg/m^2 of platinum, a dose-response risk for alkylating agents and between anthracyclines and breast cancer [24]. Several cohorts found that there was a dose-response risk of breast cancer with an exposition to anthracyclines (cumulative dose >250 mg/m^2 [50, 51]) without radiotherapy, with a SIR = 3.8 (1.7–8.3) and hazard ratio = 3.1 (1.4–6.5), particularly in patients with Li-Fraumeni syndrome or after a sarcoma or a leukemia [51, 52], but the impact of anthracyclines was not found in all the cohorts and new research is ongoing [53].

Alkylating agents are also a risk factor for lung cancer after Hodgkin lymphoma [54]. Within a population-based cohort of 19,046 patients with Hodgkin lymphoma (diagnosed from 1965 to 1994), a case-control study of lung cancer was conducted among 222 patients who developed lung cancer and for 444 matched control patients. The risk of lung cancer was similar for patients who received alkylating agents without radiotherapy and radiotherapy <5 Gy (RR: 4.2; 95% CI [2.1–8.8] and RR: 5.9; 95% CI [2.7–13.5], respectively). In this same study, the risk increased with the dose of alkylating agents and dose of irradiation. In comparison with t-AML and secondary cancer following radiotherapy, the risk was significant within 1–4 years after alkylating agents and after a longer delay (≥5 years) after irradiation.

Alkylating agents are also considered a risk factor for thyroid cancer after childhood cancer, with this risk interacting negatively with irradiation, by decreasing from RR: 10 in those with childhood cancer who did not receive radiotherapy to RR: 0.9 (i.e., no risk) in those who received more than 20 Gy to the thyroid [55].

Procarbazine has been pointed out in several studies to significantly increase the risk of colorectal cancer among both childhood and adult cancer survivors [56, 57]. In the CCSS, in a multivariate analysis, procarbazine with a cumulative dose >7036 mg/m^2 and platinum were found as significant risk factors [57]. The same results have been published in the St. Jude cohort, including a significant impact of alkylating agents [58].

In conclusion, the association between chemotherapy and second cancers is well known for t-AML (principally, alkylating agents, and topoisomerase II inhibitors), and several studies have described an increased risk for solid cancers in both childhood and adult cancer survivors. The concerned molecules were often platinum compounds, alkylating agents, and inconsistently, anthracyclines (particularly for some specific patients, such as patients with Li-Fraumeni syndrome).

Radiotherapy

Radiation-induced cancers have been known since the beginning of radiation therapy. Progress in radiotherapy, particularly since the end of the twentieth century, has led to the possibility of providing escalating radiation doses to the tumor while sparing the healthy surrounding tissues. But, secondary cancers remain a problem. In a registry study involving 647,672 cancer patients (oral and pharyngeal/salivary gland/rectal/anal/laryngeal/lung/soft tissue/female breast/cervical/endometrial/prostate/testicular/eye and orbital/brain and CNS/thyroid cancers) with an average

follow-up of 12 years and treated from 1973 to 2002, 60,271 (9%) developed a second solid cancer. The relative risk was calculated with Poisson regression adjusted for age at diagnosis, attained age, stage, gender, and year of diagnosis, and only a small part of these second cancers (8%) (95% CI [7–9]%) could be related to radiotherapy, meaning 5 excess cancers per, 1000 patients treated with radiotherapy by 15 years after diagnosis [2]. Radiotherapy during childhood/young adulthood is an established risk factor for second breast/thyroid/digestive/cutaneous cancers [59]. Among survivors receiving radiation treatment, the relative risk of developing a subsequent neoplasm is 2.7; 95% CI [2.2–3.3]. These neoplasms most frequently occur within the radiation field. Several factors related directly to the radiation treatment can modify the risk, in addition to host factors and concomitant or adjuvant medications. In the future, host factors will become more and more important and will probably change our recommendations to better screen the patients at higher risk [60, 61]. Recent data coming from a discovery study done in the CCSS suggest associations between secondary cancer linked with radiotherapy and potentially protein-damaging rare variants in genes involved in DNA double-strand break repair, particularly homologous recombination repair gene variants (with an odds ratio of 2.6; 95% CI [1.7–3.9]) [61].

Age

Radiotherapy during childhood leads to a tenfold risk of secondary cancer compared to that during adulthood [62, 63]. In the study published by Berrington et al., the relative risk of secondary cancer increased with younger age at treatment, larger treatment fields, and time since diagnosis and decreased with increasing age at diagnosis [2]. Regarding patients treated during childhood or young adulthood, young age at the time of treatment remained a risk factor [5, 19, 20, 51, 64, 65]. Added to this young age, for breast cancer, the risk is also increased when radiotherapy is delivered during puberty or around pregnancy [66, 67].

Dose

In most of the organs, the risk of secondary cancer increased with the dose received, with two exceptions—the thyroid and kidney [53, 63, 64, 68, 69]. Nevertheless, small doses of irradiation are known to increase the risk of cancer, for example, from radiological exams. Modern radiotherapy techniques, including intensity modulated radiation therapy (IMRT), can deliver highly conformal dose distributions, allowing a higher dose with better homogeneity in the target volume while reducing doses to normal tissues within the irradiated volume, but it leads to a larger volume of distant tissues receiving low-to-moderate doses (<1 Gy). Currently, in a recent review of the literature, there was neither proof from clinical nor epidemiological studies about a possible role of high-dose gradients in surrounding organs or an increased risk because of increasing volumes of distant tissues exposed to low

doses [13]. Concerning the risk of thyroid cancer after radiotherapy, with a specific dose-response risk (plateau between 10 and 30 Gy and a decreasing risk at higher doses but remaining significantly higher), the hypothesis is that it could be due to killing cells. These observations from several studies were confirmed in an international pooled analysis of 12 studies about thyroid cancer in survivors of childhood cancer [69]. In this same analysis, the strongest dose responses were seen for those who were youngest at the time of the treatment, and the chemotherapy had an additive effect. At very low doses (<0.2 Gy), the risk remains significant for thyroid cancer with a dose relation that is inconsistent [69, 70]. In adult cancer survivors, radiotherapy seems to not be a risk for thyroid cancer [17, 71].

Increased dose by session has also been found to increase the risk, but few data have converted an equivalent dose to compare this characteristic [72].

Cohort studies concluded that the lifetime cumulative risk of breast cancer was 10–33%, depending on the dose received by the breast, compared with 11–12% in the general population. In the CCSS cohort, among the 1230 female survivors exposed to chest radiotherapy, the cumulative incidence of breast cancer was 30% by age 50 and increased at 35% among survivors of HL, which is comparable to that of BRCA mutation carriers in the general population [63]. This is consistent with other studies done in childhood cancer survivors or in Hodgkin lymphoma survivors [64–68].

Skin cancers, mainly basal cell carcinomas, are the second most common cancers in cancer survivors (430 non-melanoma skin cancers out of 1160 s cancers in the CCSS cohort, at a median age of 31 years (range 11–46 years) and 83% of subjects were first diagnosed with basal cell carcinoma between 20 and 39 years of age, with a median delay with the first cancer of 18.2 years (range 5.2–29.6 years)) [23, 73]. Melanoma, less frequent but more serious, represents, according to the series, about 4% of second cancers. The incidence is low (incidence: 0.55% (0.37–0.73) at age 35) but the relative risk is very high. In a CCSS study of 14,358 patients, 57 melanomas in 51 patients were diagnosed within a median time of 21.0 (5.6–35.4) years after the initial diagnosis and at a median age of 32.3 (10.9–49.0) years [74].

Adult cancer survivors treated before 30–35 years of age with radiation therapy have a 40-fold increased risk of developing squamous cell skin cancer and more than 2.5-fold increased risk of developing melanoma compared to the general population [23, 59, 73–76]. In multivariate analysis including the type of primary cancer, gender, ethnicity, and year of diagnosis of primary cancer, radiation doses equal ≥1 Gy were associated with an increased risk of BCC, with an increased odds ratio of 1.09; 95% CI [0.49–2.64] per Gy [73]. The odds ratio for subjects who received ≥35 Gy at the skin site compared to those who received no radiation therapy was 39.8; 95% CI [8.6–185]. With respect to the proximity of the BCC to the radiotherapy field, the highest risks were associated with sites within or immediately surrounding the treatment field (<3 cm; OR: 3.1; 95% CI [1.1–9.2]) compared with those who received no radiotherapy. In a case-control study including 57 cases of skin melanoma having occurred after cancer in adulthood and 171 controls matched on gender, age, type of first cancer, and follow-up, no excess risk of melanoma was associated with radiotherapy (OR for 1 Gy: 1.01; 95% CI [0.96–1.07]) or

hormonotherapy, whereas chemotherapy (OR: 2.3; 95% CI [0.93–5.6]) and having a history of familial cancer (OR: 2.8; 95% CI [1.3–5.9]) exhibited a nearly significant risk [77].

In a CCSS case-control study, survivors who received ≥35 Gy to the skin were at a significantly increased risk, with an OR of 39.8, 95% CI [8.6–185]. The risk was also significantly increased with small dose exposure, from 1 Gy, and increased with the dose [1–4.9 Gy, RR: 3.6; 95%CI [1.4–9.1]; 5–14.9 Gy, RR: 11.7; 95% CI [4.9–27.9]; 15–24.9 Gy, RR: 14.9; 95% CI [6.0–37.3]; 25–34.9 Gy, RR: 22.2; 95% CI [7.5–65.8]; and 35–63.3 Gy, RR: 39.8; 95% CI [8.6–185]. Other risk factors for skin cancer include full body irradiation and allografts, particularly if there was acute or chronic graft versus host disease.

Without listing all the secondary cancers, radiotherapy has been found to significantly increase the risks for digestive cancer, sarcoma, lung cancer, and meningioma and has already been described as having a dose relation risk and an inverse link with age at exposure. For example, the relative risk of colorectal cancer in survivors treated with abdominal/pelvic radiation therapy has been found to be 4.5–25 times higher than that of the general population. The range of risk is very large and depends on the follow-up duration and prior cancer treatment. Moreover, as we expect a low rate among a young population, small changes in the observed number of colorectal cancers lead to a significant variation in estimated relative risks [57, 58, 78–80]. Not only childhood cancer survivors are concerned by this risk. In a recent article by van Eggermond et al. [56], in a cohort of 3121 5-year Hodgkin lymphoma survivors treated between 1965 and 1995, with 41.2% under the age of 25 at first cancer, after a median follow-up of 22.9 years, 55 patients developed CRC, and the SIR was 2.4 (1.8–3.2). The highest risk was seen for inverted-Y field radiotherapy in the area of the transverse colon. A cumulative procarbazine dose >4.2 g/m^2 was associated with a 3.3-fold higher CRC risk; 95% CI [1.8–6.1] compared to treatment without procarbazine, and procarbazine associated with infradiaphragmatic radiotherapy had a hazard ratio of 6.8; 95% CI [3.0–15.6] compared with patients receiving neither treatment. More recently, data from the FCCSS, after estimation of the dose received at the site of the digestive anthracyclines for patients treated with <30 Gy, after controlling for radiotherapy and MOPP regimen [78]. Secondary digestive cancer during the first 40 years after childhood radiotherapy is rare, but the morbidity is important; when taking at a small stage, the survival rate is high, justifying screening strategies among high-risk persons. Concerning the risk of meningioma, the risk increased with the dose and was particularly significant for a dose ≥20 Gy [81–83]. The cumulative incidence of a second cerebral tumor is estimated to be 3.6% at 40 years of follow-up since a diagnosis of childhood or adolescent cancer, but the risk is increased 50–100-fold after cranial radiotherapy versus without, with a median latency of 10–25 years [81]. In the CCSS, 199 meningiomas in 169 former patients were identified among 4221 survivors exposed to cranial radiotherapy (>1.5 Gy), with a median delay from exposure of 22 years (5–37 years) [82]. The cumulative incidence at the age of 40 years was 5.6%; 95% CI [4.7–6.7]% and the risk was significant for a dose ≥20 Gy (HR (20–29 Gy): 1.6; 95% CI [1.0–2.6] and HR (≥30 Gy): 2.6; 95% CI [1.6–4.2]). The

morbidity and mortality are significant with neurologic sequelae, such as seizures, auditory-vestibular-visual deficits, focal neurologic dysfunction, and severe headaches. In the CCSS, 13% of patients were deceased, with a median follow-up of 72 months after meningioma diagnosis.

Concerning the risk of developing secondary sarcoma, a higher dose is usually necessary with a 30-fold higher risk after 44 Gy compared to that with 14 Gy [24, 63, 80, 84, 85]. In the CCSS case-control study, radiotherapy was a risk factor for secondary sarcoma, with an OR of 15.6; 95% CI [4.5–53.9] for 10–29.9 Gy, which increases to 114.1; 95% CI [13.5–964.8] for doses >50 Gy [86].

Size of the Field

The risk of secondary cancers increased with increasing radiation field size [87]. The impact of the field has been well studied for Hodgkin lymphoma, leading to a reduced field in the modern treatment area. For example, for patients treated for Hodgkin lymphoma compared with the age/sex-matched general population, the relative risk for patients treated with mantle radiation alone was 2.1 versus 4.2 and 5.1, respectively, for the ones treated with subtotal and total lymph node irradiation [88]. Again, among Hodgkin lymphoma survivors, in a cohort of 1112 women treated before the age of 41 years, full mantle irradiation increased the risk of breast cancer by 2.7-fold compared with that of mediastinal irradiation alone (hazard ratio, 2.7 (1.1–6.9)) [89]. This was confirmed in a meta-analysis with a threefold decrease of breast cancer with a smaller field (involved field versus extended field) [90] and after in a review of the literature made by an Inserm unit [91]. Another study done by Journy et al. highlighted the importance of the field for breast cancer survivors and the risk of second oesophageal cancer [13].

When Adding Several Risk Factors

In several studies, the effects of radio- and chemotherapy were additive, whereas the effects of radiation and smoking seem to be multiplicative. This additive effect was, for example, found in the international pooled analysis of thyroid cancer among childhood cancer survivors [69]. Several studies analyzed the risk of lung cancer in Hodgkin lymphoma survivors (adult and pediatric). Authors found an additive risk when patients were exposed to radiation and alkylating agents but found a multiplicative relationship between radiation and smoking (increased risk >20-fold) [54, 92]. In other cases, the impact of chemotherapy was inferior to that of radiotherapy most of the time and was emphasized with small or medium doses of irradiation, principally alkylating agents and anthracyclines. For example, in the CCSS, including 12,756 patients to study second thyroid cancer for patients who received <20 Gy to the thyroid, both alkylating agents and anthracyclines increased thyroid cancer risk (with a RR of 2.4; 95% CI [1.3–4.5] and a RR of 1.8; 95% CI [1.1–3.1], respectively), and these molecules were not significant for patients not treated with

radiotherapy or for whom the dose was >20 Gy [93]. In another study done on 4438 patients of the French Childhood Cancer Survivor Study, de Vathaire et al. showed that nitrosoureas (BCNU or CCNU), classified as alkylating agents, increased the risk of second thyroid cancer with a RR of 6.6; 95% CI [2.5–15.7] [94].

Concerning skin cancer, common characteristics that indicate sun sensitivity, such as hair and skin color, increase the risk of basal cell carcinoma in cancer survivors [73, 95].

Hormonal status influences the risk of second cancers. Premature menopause decreases the risk of breast cancer [89, 96]. Tamoxifen increases the risk of endometrial cancer (OR: 1.52; 95% CI [1.07–2.17]), with this risk increasing with the duration of the treatment (particularly when used more than 5 years, OR: 4.06; 95% CI [1.74–9.47]) compared to that in non-users [97]. The impact of irradiation to the pineal gland should be more deeply investigated, as the results are inconsistent. For example, in the FCCSS, pituitary irradiation decreased the risk of thyroid cancer [94].

In conclusion, radiation exposure is an established risk factor for secondary neoplasms with a strong relationship with the dose (even if not always in a linear way) and size of the field, as well as an inverse relationship with the age at the time of treatment.

Screening

All these studies describing late complications linked to specific therapeutic exposures enable the characterization of groups at high risk. Health screening is an effective way to detect a particular condition or disease early, before any signs or symptoms, and is of clinical interest when early detection leads to gain of survival or decreased risk of morbidity. To be relevant, the disease targeted by the screening should be an important health problem, and the existence of an easy, acceptable, reliable, sensitive, cost-effective, and (if possible) quite specific test should be necessary. Concerning secondary cancers, several studies have described the risk factors, but data concerning the optimization of screening strategies are limited, mainly due to ethical concerns (difficult to propose a randomized strategy of screening versus none). As mentioned before, because of the rarity of some second cancers or of the absence of an adequate exam, even if the RR is significant and sometimes very high (>10), recommendations for cancer screening do not exist for all localizations.

Most of the recommendations extrapolate data about screening strategies from the general population or already known group of high-risk cancers (for example, BRCA mutation and breast cancer screening programs or APC mutation or polyposis and colorectal cancer screening programs), but clinicians must consider the eventual harms of a screening strategy, including psychological distress and overdiagnosis, particularly for thyroid cancer.

Several scientific societies have developed survivorship guidelines particularly for childhood cancer survivors, including the Children's Oncology Group (COG)

[98–100]; European societies, such as the Scottish Intercollegiate Guidelines Network (SIGN) [101], the Late Effects Group of the United Kingdom Children's Cancer and Leukaemia Group (UKCCLG) [102], the Dutch Childhood Oncology Group [51], the French society SFCE [103, 104], or the Swedish one [105], as well as in adulthood cancer survivors where screening guidelines are emerging [12, 39, 106–108]. An overview of several of them is presented by Landier et al. [99]. An international Late Effects of Childhood Cancer Guideline Harmonization Group with the Pan-European Network for Care (PanCare) [109] has an objective to harmonize these recommendations internationally using systematic literature searches, leading to rigorous evidence-based summaries [110–112]. Due to the limited trials on screening strategies, the guidelines define survivors at high risk from data in the literature and then try to define a consensus to formulate the screening strategies in collaboration with different experts (epidemiologists, radiation oncologists, pediatricians, and pediatric medical subspecialties) and patient advocates [113]. As presented before, many scientific societies recommend personalized screening for cancer survivors; however, in the absence of a program, these recommendations are not followed [65, 108, 114–119].

In general terms, all former patients should be advised to inform their health care provider if they detect a mass in an organ, a prolonged pain, a wound that does not heal, or symptoms that linger (>1 month) without explanation (fever, dyspnoea, altered general condition, digestive disorders, and bleeding).

Concerning therapy-related leukemia, there is no real strategy of screening because of the absence of a recognizable or early symptomatic stage. Nevertheless, clinicians counsel survivors to promptly report any unusual fatigue, pallor, petechiae, or bone pain [120].

Concerning the risk of breast cancer, a recent update has been published [53]. Breast cancer screening is recommended annually for women treated with ≥10 Gy chest radiation (strong recommendation), also including upper abdominal radiation at a young age, which may expose breast tissue to a significant dose (moderate recommendation). The screening strategy is based on mammography and breast magnetic resonance imaging (MRI) annually up to at least the age of 60 years. Because of a lack of evidence and inconsistent data, breast cancer screening is not recommended for women treated with anthracyclines without radiotherapy [53]. Nevertheless, authors suggest testing for genetic cancer predisposition syndromes, such as Li-Fraumeni syndrome, and for survivors of leukemia, CNS tumors, and non-Ewing sarcoma who have been treated with high-dose anthracyclines. Although breast cancer risk is increased in men after radiotherapy, screening is not recommended for them because of its rarity, even if they received radiotherapy exposing the breast tissue [121]. Premature ovarian insufficiency reduces the risk of secondary breast cancer (level A evidence), but data are insufficient to calculate the exact level of reduced risk. For the moment, it cannot be taken into account whether or not to recommend breast cancer screening, as most of these women receive hormonal treatment. In the harmonization guidelines, while taking into account the potential harms (risk of false-positive results leading to emotional distress and additional imaging and biopsies, risk of overdiagnosis, burden of regular surveillance, and the

risk of potential radiation exposure from radiological exams (mammography)), experts concluded that, for women who received ≥10 Gy to the breast tissue, the benefits of screening an attained age of 25 years or 8 years after radiation, whichever occurs last, at least up to age 60 years with annual mammography and MRI are expected to outweigh the harms. The authors added that, in some circumstances, just one exam could be realized. Therefore, for example, in France, experts recommend to avoid mammography before the age of 30 and to limit the irradiation by doing a single external oblique incidence mammogram using digital technology [108, 122, 123].

Concerning the risk of thyroid cancer, the impact of radiotherapy among childhood cancer survivors is consistent but in larger epidemiological studies, even if the risk is elevated after a range of first primary adult cancers. The link with the first treatment is not obvious, and screening may contribute to its elevation [17]. Balancing the benefits and harms of cancer screening is important. This is a major concern with thyroid cancer, as there are not any randomized trials evaluating if earlier detection of thyroid cancer by screening impacts morbidity and mortality, because the risk of overdiagnosis is greater than for other cancers (indolent cancer which might never cause clinical problems), and because of the risk of the detection of benign nodule(s), which can lead to repeated exams, fine-needle aspiration biopsies, or thyroid surgery. Nevertheless, evidence from studies of adults indicates that an advanced stage is a risk factor for recurrence and mortality [124]. Additionally, an early stage usually leads to a less extensive surgery and no or lower doses of radioactive iodine therapy. Indirectly, many scientific societies recommend screening for former patients at high risk. In this aim, the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCareSurFup Consortium did an exhaustive review of the literature recently, and their conclusions highlight the need for shared decision-making with the former patient whether or not to undergo thyroid screening and in the choice of the modality, as of the two available (thyroid ultrasound and neck palpation), none was shown to be superior [124]. Insufficient data exists concerning thyroid cancer risk after chemotherapy. Also, experts recommend that former patients treated with radiation therapy, including the thyroid gland or just nearby or probably those with therapeutic 131I-MIBG, should be counseled regarding their increased risk for developing thyroid cancer.

Concerning skin cancer after radiotherapy, there is not a specific strategy. Patient education is important to avoid supplementary risk factors. As in the general population, basal cell carcinomas are the most frequent and the least serious due to their development, which remains local. Their complete removal ensures the patient's recovery. The interest in early detection facilitates the removal and reduces the esthetic risk because these cancers can spread on the surface. Recent evidence indicates that early diagnosis of basal cell carcinomas can lead to smaller tumors, potentially less extensive treatment, better outcomes, and lower treatment costs [125]. Squamous cell carcinomas are rarer and more aggressive because they can invade lymph nodes and metastasize. The value of screening is to allow early detection at a local stage. For cutaneous melanomas, as in the general population, any delay in

diagnosis can lead to unnecessary morbidity and even mortality [126]. Indeed, melanoma has a good prognosis if detected early enough (Breslow index <2 mm and no metastases), and treatment consists of surgical excision (relative 5-year survival is 98% at the localized stage). When lymph node involvement is present, survival decreases to 62% and drops to 15% at the metastatic stage. Approximately 20 years after radiotherapy, when most of these patients are in their 30s, this population faces the possibility of skin cancers—multiple and recurrent and at rates much higher than those of the general population of the same age. The COG, National Cancer Institute and some other expert groups, such as the National Cancer Institute and long-term follow-up committee of the SFCE, recommend an annual dermatological examination to detect skin cancer at an early stage in pediatric and young adulthood cancer survivors who have received radiation therapy. But, no study has evaluated the best frequency of this screening, the optimum period to start, or other strategy based on empowerment, as comparison between self-examination and patient education and an early access to a specialist if needed versus a regular exam by a professional. However, the literature reports that less than one-third of survivors of pediatric cancer have ever had a clinical skin examination by a physician [127–129].

The increase in the risk of colorectal cancer is high after abdominal radiotherapy or after procarbazine exposure, but it is still a rare complication. On the other hand, the survival of patients with colorectal cancer depends on various prognostic factors, including the stage of cancer, lymph node involvement, presence of metastases, early treatment, depth of parietal invasion, and existence of an invasion by neighboring bodies. Clinical guidelines are inconsistent regarding the early initiation of surveillance in these patients due to the lack of supporting evidence of the oncogenesis of colorectal cancer after radiotherapy. The COG recommends screening based on colonoscopy every 5 years after delivery of abdominal radiotherapy ≥30 Gy when the survivor has reached 35 years of age and/or after high-dose procarbazine (2.8 g/m^2), which is based on the recommendations of CRC screening in high-risk populations because this exam can detect and remove early precursor lesions. Probably because of the exam, which is invasive, digestive screening is not a current practice in all countries [78, 129]. Nevertheless, even in the CCSS, adherence is not optimal (29.5%) [130]. Recent data from the FCCSS suggest some modifications to define the target population, as 42 out of 5015 patients treated with radiotherapy during childhood who developed colon cancer, 28.6% were <35 years old [78]. Moreover, the estimated dose received by 50% of the abdomen was >30 Gy for only one patient, and the estimated dose received by 20% of the abdomen was >20 Gy for 43% of patients and >30 Gy for 7% of patients. Other studies are consistent with these results and suggest to perform screening for patients at the age of 30 years or after a delay of 5 years after exposure, whichever occurs later, and who received ≥20 Gy by colonoscopy or multitarget stool DNA test every 3 years [131, 132]. Although the COG and some other expert groups recommend early CRC screening for patients with prior abdominal radiotherapy, the effectiveness of early screening is unknown. Despite recognizing the increased colorectal cancer risk, other relevant guideline resources do not explicitly recommend the early initiation of colorectal cancer screening in childhood cancer survivors. It is also unknown if

the oncogenesis is the same as in primary colorectal cancer, meaning if the radiation-induced colorectal cancers pass through precancerous polyps, which are detectable and treatable, prior to becoming invasive cancers. In a recent study of cancer survivors, with 72 enrolled patients, 24 patients (44.4%; 95% CI [32–57.6%]) were found to have 49 polyps, of which 8 patients had >1 adenomatous polyp and 15 patients had precancerous neoplastic polyps (tubular adenoma, tubulovillous adenoma or serrated adenoma) [132]. This polyp prevalence is at least as high as that previously reported for the average-risk population aged ≥50 years and very similar to the 24% rate reported in a study of patients at risk for hereditary non-polyposis colon cancer undergoing their first colonoscopy screening [133]. These studies give evidence that the prevalence of screening detectable polyps in young cancer survivors treated with abdominal/pelvic radiotherapy is comparable to that in other groups for whom screening is recommended. The other strategy could be based on fecal occult blood testing and may be potentially more acceptable among these survivors [134, 135]. The risk of a false-positive test does not seem to be increased, even after infradiaphragmatic radiotherapy, because few people suffer from anemia due to potential intestinal mucosal alterations [136]. In a study analyzing 871 patients with Hodgkin lymphoma in remission treated with chemotherapy, radiotherapy, or both (36%, 40%, and 24%, respectively) and after a median follow-up of 12 years, authors calculated an average excess of 22.8 cases of colorectal cancer per year among 10,000 patients and recommended a fecal occult blood test once a year and colonoscopy whenever any suspicion arises [137]. Actually, the international Late Effects of Childhood Cancer Guideline Harmonization Group is working on an exhaustive review of the literature with the aim to write international recommendations on colorectal cancer. Acceptability is a major variable that must be included in the reflection of the screening strategy.

Concerning the risk of second cerebral neoplasms, the COG does not recommend regular screening, except for patients with neurofibromatosis beginning 2 years after radiotherapy. The SFCE recommends an MRI every 5 years.

Conclusion

Data from the literature among childhood and adult cancer survivors clearly supports the role of oncologic treatment in the development of secondary neoplasms. The impact of the treatment is higher among childhood cancer survivors for all types of secondary neoplasms. Nevertheless, interindividual variability exists, suggesting the impact of environmental exposure and genetic susceptibility combined with specific high-risk polymorphisms or gene-environment interactions. All cancer survivors should be counseled to decrease the risk of second neoplasms and for some to follow screening recommendations that take into account the different treatments, such as chemotherapy, radiotherapy, and hormone therapy. Additional research is needed to better understand the role of specific chemotherapeutic agents, including the new classes of anticancer agents, individually and in combination with other anticancer agents, with radiotherapy or with environmental exposure. In

the future, clinicians will also have to consider genetic susceptibility with the aim to personalize the different screening strategies. In most of the screening recommendations, targeting former patients is mainly based on irradiation data because of the lack of informative data about molecules. Moreover, large datasets, probably through international collaborations, are needed to provide robust analyses, answer persistent questions, and understand inconsistent results.

To increase the adherence of several screening protocols for the same patient, acceptability must be taken into account, and the notion of "empowerment" seems to be suitable and effective [115, 138, 139]. Empowering patients means strengthening the ability of patients to act effectively on the determinants of their health while promoting their independence and quality of life.

In conclusion, because of great advances in treatment options, cancer survival rates are improving and long-term follow-up strategies are becoming more and more important. The goal and grail in research into cancer aim to better understand, prevent, and treat late-occurring effects while preserving and still increasing long-term survival. A summary of treatments with detailed recommendations for screening and advice for lifestyle is necessary for each cancer survivor. Second cancers are multifactorial, with key roles played by primary cancer treatments and genetic susceptibility without forgetting lifestyle factors and environmental exposures.

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Specific Issues of Children and Young Adults in Survivorship Care

16

Pierre Contant and Charlotte Demoor-Goldschmidt

Introduction

Pediatric and young adult oncology is a multimodal medical discipline justified by the age of the patients, specificity of the pathologies, and particularities of the pediatric approach, integrating the post-cancer issue with the diagnosis. These disciplines face two major challenges: to heal more, due to the contribution of new therapeutic approaches (i.e., targeted therapies, immunotherapy); and also to heal better, in order to preserve the quality of life of the treated patient, by reducing the side effects of the treatments used as much as possible. For a long time, the unique goals of treatment were healing. These objectives have been maintained, and in addition, doctors taking care of these children also work on de-escalation of treatments and the after-effects that should be avoided.

Currently, approximately 50,000 new cases of cancer in people under 25 years of age are diagnosed in the European Union each year [1, 2]. The progress made in recent years in the global management of pediatric cancers (diagnosis, extension assessment, anticancer treatments) has considerably improved the survival of these patients. Outcomes of childhood cancer have shown significant improvement due to the progress in multimodal therapy (including new chemotherapy regimens, modern radiotherapy techniques, optimized supportive care) and 5-year survival rates are currently above 80% in western European countries and the United States (US)

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[3–13]. Nevertheless, cancer remains the main cause of disease-related mortality in children justifying aggressive treatment. It is estimated that in 2020, 500,000 persons are childhood cancer survivors (CCS) in the US, meaning that 1 of 750 individuals is a CCS, whereas in France, for example, it affects 1 of 440 individuals [14, 15]. As a result of this successful outcome, it has become essential to consider the morbidity and mortality associated with cancer treatments. Survivors are indeed at risk of developing a series of adverse effects. Also, recent publications show that the number of deaths in the population of patients cured of childhood cancer is 11 times higher than that of the general population. The increasing number of patients cured of cancer in childhood and adolescence, and highlighting the risks of complications and after-effects, have focused the need to establish a personalized post-cancer program and to organize the prevention and long-term management of these patients.

In this article, we will describe the increased risk of young mortality and health complications which can affect the quality of life of adult childhood and young adulthood cancer survivors (YACS) [14, 16, 17].

Morbidity

Abundant research studies describe long-term adverse outcomes involving physical health, including growth and development, organ function, reproductive capacity, and risk of subsequent carcinogenesis but also metabolic dysfunction, psychological issues, and neurocognitive deficits.

An increase in survival rate is not without cost to the cured child/young adult. Several publications described cumulative prevalence rates between 40–84% of long-term sequelae due to their cancer and its treatment, which can be disabling and/or life-threatening [18–23].

The most prominent causes of late mortality are the development of subsequent primary cancers and cardiovascular problems [24].

The risk of second cancer depends on several factors, mainly extrinsic (chemotherapy, radiotherapy) and intrinsic (age at diagnosis of first cancer, sex, genetic predisposition). In the US, approximately 89,500 new cancer cases among people aged 15–39 years were diagnosed in 2020, and the probability of developing invasive cancers before the age of 40 is 1:70 among males and 1:48 among females [1, 2]. As an example, Oeffinger et al. found the cumulative incidence of breast cancer at age 50 to be 30% with an incidence of 35% in Hodgkin's lymphoma survivors, similar to patients carrying the BRCA1 gene [25]. Reulen et al. evaluated the cumulative incidence of development of a second colorectal cancer in survivors treated by abdominopelvic irradiation in pediatric oncology [26, 27]. This risk was comparable (1.2%) in individuals with at least two first-degree relatives with colorectal cancer (population at high risk of developing colorectal cancer).

After secondary cancers, heart disease is the second most common and severe long-term complication of treatment. The prevalence of cardiotoxicity attributable to treatment varies from 0 to 16% when only heart failure criterion is considered but reaches 57% when subclinical cardiac dysfunction criterion is considered. Moreover,

cardiac pathologies after childhood cancer are the second leading cause of organ transplantation (0.49% cumulative incidence 35 years after cancer) [28]. The median time to onset of heart disease is 19.5 years with a cumulative incidence, at 30 years of diagnosis, of severe to lethal cardiac pathology of 4–5%, but 11% for all grades. At the age of 45 years, coronary pathology or heart failure is detected in 5% of patients, and a valve anomaly or arrhythmia in 1–2% (with a relative risk around 10) [29–38]. After Hodgkin's disease, a cumulative incidence of grade III–V cardiac pathologies of 45.5% was described at the age of 50 years, while in the general population, incidences of heart failure of 0.35% and cardiac pathologies of 3–6% were found [39]. Anthracyclines (including different molecules) [40] and mediastinal radiotherapy are the two main cardiotoxic treatments that contribute to this morbidity and significant long-term mortality, with a dose-effect relationship [41, 42]. If specific treatments are considered, after radiotherapy, an increase of cumulative incidence at 25 years to 21% of decreased ejection fraction for a dose of 36 Gy and 5% for a dose of 20 Gy; and after anthracyclines, a cumulative incidence at 20 years increases to 25–50%, according to multiple studies [30, 43–51]. Irradiation leads to fibrosis lesions of the myocardium, pericardium, and valves. It also alters the vessel walls and leads to atherosclerotic lesions responsible for coronary artery disease. Patients can remain asymptomatic for years and the damage can be insidious [27].

Endocrine complications are very common in adults cured of pediatric cancer, and less among YACS [52–54]. They have been subjected to treatments of chemotherapy, radiotherapy, and/or surgery, generating endocrine deficits in 30–60% of cases (50–60% after brain radiotherapy in childhood), including hypothalamic-pituitary hormone deficits, deficits in hypothalamic appetite regulation, and gonadal deficits [55–62]. These treatments also impact nutritional balance and the skeleton, affecting growth, pubertal development, bone mass, maintenance of body weight, reproductive capacity, and general hormonal equilibrium. The medical follow-up and care of these children must allow satisfactory growth, maturation, and psychosocial adaptation. The most frequent pathologies are growth hormone deficiency, thyroid pathology (between 13.8 and 20% of survivors), and menopause/early andropause, followed by diabetes and metabolic syndrome (31.8% of survivors, 46–52% post-leukemia) [41, 63–67]. Metabolic syndrome is significantly more frequent among adult cancer survivors than in the general population, and has been particularly described after breast or prostate cancer, but also other cancers, such as colorectal cancers [68–72]. At the pituitary level, all axes can be involved. Nevertheless, central diabetes insipidus is not a long-term complication, but a direct consequence of the tumor and/or surgical resection, and manifests itself in the first weeks after surgery. The most affected axis is the somatotropic axis (10–13%; up to 45–50% after brain radiotherapy).

Pulmonary sequelae include asthma, chronic cough, pulmonary emphysema, oxygen dependence, pulmonary fibrosis, and recurrent pneumonia. The cumulative incidence of any respiratory disorder at 35 years varies depending on published studies: 20–40%, and 30–50% at 45 years. The main actors of these toxicities are thoracic radiotherapy and chemotherapy, including platinum salts, bleomycin, busulfan, methotrexate, and thoracic surgery [73–76].

Renal sequelae secondary to treatment are manifested by impaired tubular and glomerular function, proteinuria, and secondary hypertension. The causes of such chronic kidney damage are varied. Sometimes the malignant disease itself can cause chronic kidney failure, for example, by damaging normal kidney tissue through tumor infiltration or obstruction of the urinary tract. Treatment-related chronic kidney damage is related to chemotherapy (i.e., methotrexate, ifosfamide, cisplatin, and carboplatin), radiation therapy, surgery, and supportive treatment (aminoglycoside antibiotics, amphotericin antifungals) [77–83]. Prevalence is highly variable between studies (0–84%), depending on the population studied, main criterion, and regression. Chronic renal failure has been documented as 2.4–32%, a decrease in the onset of glomerular filtration between 0 and73.7%, and proteinuria between 3.5 and 84%. The cumulative risk of hospitalization for urinary pathology at age 60 is 22% in survivors versus 10% in the general population [77–83]. After ifosfamide treatment, a tubular pathology occurred in approximately one out of four persons [78, 80]. Renal sequelae are the first cause of organ transplantation after cancer in childhood. In the CCSS study, of 13,318 survivors, 100 underwent 103 transplants, including 50 renal transplants [28]. The cumulative incidence of transplantation or being on the list at 35 years of diagnosis was 0.54% (95% CI, 0.40–0.67).

The central and peripheral nervous systems can be significantly affected, not only by the malignancy but also by the interventions used for treatment. Treatment is often multimodal and may include cranial irradiation, chemotherapy, transplantation, and immunotherapy, each of which carries distinct neurological risks (infection, neurovascular, central, and peripheral nervous system disease) [84–87]. Surgery is associated with a range of potential neurological complications, with damage to the posterior fossa being a common cause of morbidity in patients with cerebellar tumors following neurosurgical resection [88–90]. Cranial irradiation can cause neurological sequelae such as encephalopathy, cerebral vasculopathy, secondary brain tumors, and cognitive dysfunction [91–96]. The central neurological toxicity of cytotoxic drugs depends on their ability to cross the blood-brain barrier. Readily available drugs are those with the greatest neurological toxicity, including alkylating agents (metabolites of cyclophosphamide and ifosfamide, thiotepa and melphalan in high doses), busulfan, platinum derivatives, aracytin, and methotrexate [97]. Peripheral neurological damage is an extremely common side effect of chemotherapy and is usually a dose-dependent effect. Each class of drugs has a different mechanism of damage; for example, platinum salts more often involve large fibers while taxanes affect large and small fibers.

Neurosensory sequelae can decrease quality of life and affect taste, smell, vision, and hearing. These neurosensory impairments may be related to the toxicity of chemotherapy or direct action of radiotherapy or surgery in the treatment of craniofacial lesions. Due to the effect on taste or smell, these treatments expose the body to risks of altered nutrition, general condition, and quality of life. Hyposialy, a consequence of irradiation of the salivary glands, increases the alterations of taste and risk of dental caries. An increased risk for cataracts is present in patients who received cerebral or orbital irradiation. High doses of corticosteroids have also been described as a risk factor, especially among patients treated for acute lymphoblastic leukemia

[98, 99]. As an example, in the French cohort of post-childhood leukemia, L.E.A., after transplant conditioned by total body irradiation, 30% of cataracts were found in patients at 5 years old and 78% at 20 years old [98], among other ocular complications. In the american cohort, CCSS, other ocular sequelae were described: glaucoma with a relative risk (RR) when compared to siblings of 2.5 (95% CI, 1.1–5.7); as well as legal blindness, RR: 2.6 (95% CI, 1.7–4.0), double vision, RR: 4.1 (95% CI, 2.7–6.1), and dry eyes, RR: 1.9 (95% CI, 1.6–2.4) [99]. When the lesions affected hearing, risks for impaired school or intellectual performance and decreased social interactions existed [100, 101]. Therefore, the survivors' quality of life was impacted if left untreated. The chemotoxic agents mainly involved in hearing impairment are platinum salts [102–108], radiotherapy [109, 110], or both [111]. Hearing complications mainly occur in the first 5 years, but the incidence remains significantly higher than in the control population, regardless of time frame.

Fatigue and chronic pain are among the most common and distressing side effects of cancer treatment, more frequently after cancer during adulthood. In a study published in June 2018 by the French National Cancer Institute examining a survival 5 years after cancer, two out of three people believed they suffer from after-effects, including fatigue and chronic pain. Some interventions as physical activity, psychosocial interventions, or mind-body interventions showed some results to reduce fatigue.

Premature Mortality

Childhood Cancer Survivors

Premature mortality remains a real problem. In 2006, the Childhood Cancer Survivor Study (CCSS), a study on the largest American cohort of patients treated for pediatric cancer, highlighted these facts: overall (cumulative) mortality increases significantly over time: 6.5% at 10 years (95% CI, 6.2–6.9), 11.9% at 20 years (95% CI, 11.5–12.4), then 18.1% at 30 years (95% CI, 17.3–18.9) [24].

Premature mortality was essentially due to recurrence of original cancer (>50%), a subsequent neoplasm (10–20%) [112–116], and cardiovascular diseases (5–10%) [49, 114, 117, 118]. The order of cause mortality was consistent among the cohort (recurrence/progression of first cancer, second tumor, and cardiac disease); however, the percentage affected differed. Mortality from recurrence increased in the early years, whereas mortality from other causes continued to increase during 30–40 years of follow-up. For example, in the CCSS, in the population between 15–30 years of age, cumulative mortality due to primary disease only increased from 6.3 to 7.8%, while cumulative mortality due to late effects of treatment increased from 2.0 to 7.0% over the same period [24]. These results were supported by an English cohort study published in 2016, that was based on a population of 34,489 pediatric cancer survivors from 1940 to 2006. A total of 4475 deaths were observed, which was 9.1 (95% CI, 8.9–9.4) times more than in the general population. Among survivors aged 50–59 years, 41% and 22% of deaths were attributed to

secondary malignancies and circulatory problems, respectively, while the corresponding percentages for those aged 60 and older were 31% and 37%, respectively [19].

Recently, one comparison was conducted between the US and Europe (Great Britain). The late causes of mortality were compared between the North American CCSS and British Childhood Cancer Survivor Study (BCCSS), which are two of the largest childhood cancer survivorship cohort studies in the world [18]. The causes of death were retrieved from the data of the relevant death registries. Of the 49,822 5-year CCS (63.4% from the CCSS and 36.6% from the BCCSS), 6375 deaths were registered (n = 3924 [12.4%] from the CCSS and n = 2451 [13.4%] from the BCCSS). The cumulative mortality probabilities at 10 years from diagnosis was statistically significantly lower in the CCSS (4.7%; 95% CI, 4.5–5.0%), compared to the BCCSS (6.9%; 95% CI 6.5–7.2%), due to the lower probability of death from recurrence/progression of primary cancer. However, at 40 years from diagnosis, the CCSS had a greater cumulative mortality probability in comparison to British survivors (22.3% vs. 19.3%), attributable to a twofold higher risk of mortality from SMNs (ratio of standardized mortality ratios [RSMR], 2.1; 95% CI, 1.8–2.3), cardiac (RSMR, 1.7; 95% CI, 1.4–2.2) and respiratory (RSMR, 1.9; 95% CI, 1.5–2.6) diseases, external causes (RSMR, 1.5; 95% CI, 1.2–1.9), and other causes (RSMR, 2.5; 95% CI, 2.1–2.9). The authors suggested the differences observed may be related to treatment practices, but detailed treatment data were not available in the BCCSS.

Due to several reasons, including best management and lowering therapeutic exposure (drugs and radiotherapy), and best long-term follow-up (LTFU), we observed a decline in late mortality among 5-year CCS [119]. These reductions were attributable to decreases in the rates of death from subsequent neoplasm ($p < 0.001$), cardiac causes ($p < 0.001$), and pulmonary causes ($p = 0.04$). A decrease in the risk for subsequent malignancies was not a universal observation [120].

Adolescent and Young Adult Cancer Survivors

Few studies have focused on survivors treated for their cancer as adolescents and early young adults. A comparison was performed in the North American study, CCSS, of 5804 survivors diagnosed with cancer between the ages of 15–20 years who reached a median age of 42 years [34–50], and 5804 CCS diagnosed with cancer before the age of 15 years who reached a median age of 34 years [17, 27–42]. The standardized mortality ratios (SMR), compared to the general population for all-cause mortality, among early adolescent and young adult survivors was 5.9 (95% CI, 5.5–6.2) and among CCS, 6.2 (95% CI, 5.8–6.6). Adolescent and young adult survivors had lower SMR for death related to late effects of cancer therapy; 4.8 (95% CI, 4.4–5.1) versus 6.8 (95% CI, 6.2–7.4), respectively. Survivors had an increased risk of developing grade 3–5 cardiac (YACS: SMR, 4.3; 95% CI, 3.5–5.4 and CCS: SMR, 5.6; 95% CI, 4.5–7.1), endocrine (YACS: SMR, 3.9; 95% CI, 2.9–5.1 and CCS: SMR, 6.4; 95% CI, 5.1–8.0), and musculoskeletal conditions

(YACS: SMR, 6.5; 95% CI, 3.9–11.1 and CCS: SMR, 8.0; 95% CI, 4.6–14.0) when compared with siblings of the same age.

Decreased radiosensibility of the hypophysis among older patients has also been described in previous clinical studies. For example, in a recent evaluation comparing long-term survival outcomes and sequelae between child (n = 159) and adult (n = 477) nasopharyngeal carcinoma after intensity-modulated radiation therapy, CCS were more likely to develop grade 3–4 growth retardation and endocrine insufficiency (3.0% vs. 0.3%, respectively; $p = 0.014$) [52].

The results showed that the patterns of late mortality change over time and death by sequelae of the various treatments received 20–30 years earlier is a significant threat to this population.

Social and Psychological Effects

The consequences of cancer regardless of the age of diagnosis can affect all long-term medical health involving growth and development, organ function, fertility, and risk of subsequent tumor. Cancer experience has also been associated with an increased risk of detrimental psychosocial effects impacting mental health, socialization, educational and professional achievement, and sexuality [121–126].

Several studies suggested that 20–30% of survivors reported moderate to severe psychological distress [127]. In some studies, this value reached more than 50%. For example, in a French study, 247 of the 288 CCS who attended LTFU consultations and accepted to answer a short questionnaire. Of the respondents, 55% suffered from psychiatric issues after their cancer versus 31.9% in the general population ($p < 0.0001$): anxiety (40.5%), mood disorders (28.7%), and substance dependency (10.5%; $p < 0.0001$) [128]. Nevertheless, the risk of suicide was less for the CCS group vs. BCCS (8.9% vs. 13.6%, $p = 0.03$). This observation was also found in another study performed in North America, in which the standardized incidence ratio was 0.17 (95% CI, 0.07–0.27] of the prevalence of suicidal behaviors [129].

Oerlemans et al. showed that patients with Hodgkin's lymphoma were more anxious and depressed compared to the general population, which has a long-term impact on cancer survivors. Indeed, over a 4-year period, approximately 10% of Hodgkin's lymphoma patients reported that they were always anxious or depressed. As a result, clinicians should be aware that patients with former Hodgkin's lymphoma suffering from anxiety and depression require special follow-up [130].

Psychological distress was associated with female gender, long-term side effects, and perceived low parental support [131].

Quality of life is influenced by socio-professional integration, which refers to the notions of social relations, level of education, and employment. In the CCSS cohort, the proportion of subjects who were married at least once was slightly lower among former patients, all diagnoses combined, than in the general population [132]. In the US, there was little difference between former patients over 30 years of age and control subjects in the areas of education, employment, and access to insurance,

with the exception of patients followed for brain tumors. However, initial difficulties were reported in hiring in certain occupations and obtaining life insurance [133]. For these patients, the same observation was made in Great Britain; patients who received encephalic radiotherapy for leukemia or followed up for a central nervous system tumor had a lower level of education than others [134]. In Sweden or France, after cancer treatment before the age of 16 years, the level of education was significantly lower only for patients who had a brain tumor, and the income of this group was lower, even after excluding those receiving disability allowances [135, 136]. As an example, in France, among a total of 2406 survivors aged below 25 years who responded to the study questionnaire, when compared with national statistics adjusted on age and sex, health-related unemployment was higher for survivors of cerebral tumor vs. other cancers (28.1% vs. 4.3%; $p < 0.001$). Another finding was that other survivors had a similar or a higher occupational class than expected. Regarding occupation, a meta-analysis showed that cancer survivors treated in childhood are almost twice as likely to be unemployed as the control population. This excess risk is only significant for those who had a central nervous system tumor, and it is greater in the US than in Europe [137].

Conclusion

Survivors are vulnerable to medical and psychosocial "late effects" that are often associated with aging. Two to three in every four survivors experience a late effect of their cancer treatment, of which 37% may be life-threatening. It is therefore recommended that survivors attend LTFU care for the prevention, early detection, and treatment of late effects. Follow-up care is ideally approached globally and comprehensively, and usually interdisciplinary, and focuses on preventing or managing late effects through screening, education (survivors and general practitioners) on treatment-related complications, and should encourage preventative lifestyle behaviors. Despite developments of several strategies and utilization of follow-up organizations, young adult CCS often become disengaged from follow-up, particularly at the time of transition from pediatric to adult healthcare [138–140]. Accordingly, interventions are needed to reengage CCS into LTFU. Afterward, we have to keep in mind that the loss of follow-up is also a major challenge in the delivery of long-term care.

Treatment protocols, diagnosis, and patient initial characteristics help identify general risk factors for late side effects. Not all CCSs are at risk for late side effects and monitoring; therefore, recommendations should be risk-based. Numerous guidelines recommend lifelong care for CCS and adult cancer survivors, including International Late Effects of Childhood Cancer Guideline Harmonisation, a worldwide collaboration initiated to harmonize guidelines for the LTFU of childhood and young adult cancer survivors [139, 141–160]. In the future, this risk should be adapted to genetic polymorphism, which could make an individual more susceptible to late sequelae.

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Psychological Issues and Care of Cancer Survivors

17

Nienke Zomerdijk and Jane Turner

Introduction

Improvements in early detection, success in treating cancers, and aging of the population have led to an increasing number of cancer survivors. While some cancer survivors recover with a renewed sense of life and purpose, others experience ongoing adverse impacts on their health, functioning, sense of security, well-being, and relationships. As many as one in two cancer survivors experience significant levels of psychosocial distress [1] and may develop more serious psychological problems such as anxiety and depression. Financial hardship may also be experienced as a consequence of cancer treatment [2]. Attention to these problems is of paramount importance since they are associated with reduction in quality of life, increased healthcare service use (and potential increased associated costs), poor adherence to follow-up recommendations, and, as a result, shorter survival [3].

After completion of treatment, the intensive support and observation provided by the oncology team suddenly evaporates and can lead to survivors feeling alone or even abandoned. Patients may try to resume important social roles and activities that were put on hold during treatment including returning to work but often the survivor finds this challenging. Friends and family may feel that the person should be getting "back to normal" and fail to recognize that although the person has

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survived, they are not "good as new." Their lives are altered by a legacy of physical, psychosocial, vocational, spiritual, and economic consequences.

The problems presented by cancer and its treatment do not necessarily disappear over time, and this mandates an active approach to intervening to assist patients and ideally prevent or at least reduce the burdensome impact of these problems. The specialty of psycho-oncology is concerned with the psychological, emotional, and social needs of people with cancer and their families or carers. A primary goal of psycho-oncology is to ensure that all cancer patients and their families receive optimal psychosocial care across all phases of the cancer experience from diagnosis, through treatment, and survivorship [4]. To attain optimal outcomes for cancer survivors, it is recommended that their psychosocial needs be regularly assessed with an emphasis on living well using the best possible evidence and coordinated and integrated care [5, 6].

In this chapter, we focus on the common psychosocial issues faced by cancer survivors and their families and describe ways clinicians can respond and help them to achieve the best outcomes after cancer. The following topics are discussed in this chapter:

- the developing focus on the psychological issues faced by people with cancer;
- the key psychological issues confronting cancer survivors;
- foundation strategies to enhance psychosocial adjustment of cancer survivors;
- issues which merit more detailed focus and specialized care;
- models of survivorship care;
- the emotional impact of responding to complex issues for clinicians.

How Did We Get Here? The Developing Focus on the Psychological Issues Faced by People with Cancer

For centuries a cancer diagnosis was viewed as the equivalent of a death sentence as there was no treatment for the disease until surgical removal became possible after the introduction of anesthesia in the last half of the nineteenth century [4]. Shame and guilt were dominant emotions, combined with the fear that it was contagious [7]. Revealing the diagnosis to the patient was considered cruel and inhumane, so only the family was given the facts and the prognosis. This was viewed as an acceptable "white lie" but it left the patient feeling isolated and alone. In some countries, the practice of withholding the diagnosis of cancer continues, but the tendency toward open disclosure increases as patients become more informed about health and illness.

Several historical factors have led to a greater emphasis on psychosocial issues in cancer. The American Cancer Society, formed in 1913, established educational programs encouraging people to seek consultation for symptoms suggestive of cancer. This was an important first step in educating the public about the warning signs of cancer and the importance of not delaying presentation because of fear and

fatalistic attitudes. By the twentieth century, radiation and chemotherapy joined surgery to successfully treat previously fatal cancers. Attitudes evolved as cancer became more treatable, and therefore opened the door for more open discussion about the psychological issues.

In 1984, the International Psycho-Oncology Society (IPOS) was founded with the aim of fostering international multidisciplinary communication about clinical, education, and research issues that relate to the subspecialty of psycho-oncology. The Society sought to provide leadership and development of standards for education and research on the psychological, social, and spiritual factors that affect the quality of life of cancer patients and their loved ones during the continuum of the cancer illness, including survivorship. The aims of IPOS are to foster training, encourage psychosocial principles and a humanistic approach in cancer care, and to stimulate research and development training, so psychosocial care may be integrated with all clinical oncologic specialties for optimal patient care.

In 2014 the "Lisbon Declaration: Psychosocial Cancer Care as a Universal Human Right" was endorsed by IPOS. Subsequently, the IPOS Standard on Quality Cancer Care, endorsed by 75 cancer organizations worldwide, has been updated and now includes three core principles [8]:

1. Psychosocial cancer care should be recognized as a universal human right;
2. Quality cancer care must integrate the psychosocial domain into routine care; and
3. Distress should be measured as the sixth vital sign.

Despite the tremendous activities around the world that have contributed to the growing recognition of psychological issues facing cancer patients and expanding education and research efforts, attitudinal barriers have not entirely disappeared. There is still a pervasive fear that attends a diagnosis of cancer: fear of death, pain, loss of independence or attractiveness, and the suffering associated with progressive illness [4]. Patients with cancer today may fear being labeled not only as a person with cancer but as a person who needs psychological help. Stigmatization from being labeled as having a psychological problem or as being unable to cope with the disease continue to pose barriers to the integration of psychosocial oncology into oncological care.

Importantly, psychosocial cancer care is not available regularly to all patients around the world, with significant disparities evident in low- to middle-income countries [9]. The World Health Organisation predicts that in 2020 as many as 70% of the 16 million annually diagnosed cancer patients will be in developing countries [10]. These startling prevalence rates are likely related to under-developed health systems, poor health-seeking behaviors, poverty, low health literacy rates, and cultural practices. These factors make cancer care a significant challenge in low- to middle-income countries, resulting in a greater need for psychosocial care. Unfortunately, because of fewer resources, those patients with greatest need may not be able to access psychosocial oncology care.

Living Beyond Cancer: The Shifting Focus from Cancer Patient to Cancer Survivor

The transformation of cancer from a largely fatal disease to one in which a large proportion of those diagnosed are effectively treated has led to increased survival. In parallel with this improvement has been a shifting focus from the cancer patient to the cancer survivor, leading to increased recognition of the hidden disabilities that may follow the treatment of cancer [11]. Subsequently, there has been growing awareness of the physical and psychosocial late effects, which led to the recognition of cancer survivorship as an important aspect of care.

The definition of cancer survivorship has been widely debated [12]. In recent years, a variety of definitions have been proposed. Generally speaking, "cancer survivor" is used to describe individuals throughout the cancer trajectory: "An individual is considered a cancer survivor from the time of diagnosis, through the balance of his or her life. Family members, friends and caregivers are also impacted by the survivorship experience" [11]. People with advanced disease which is likely to be life-limiting also consider themselves to be survivors, and indeed there is increasing conceptualization of cancer as a chronic disease. The term "cancer survivorship" is commonly used to refer to a distinct phase in the cancer trajectory between primary treatment and cancer recurrence or end of life.

Many alternatives have been suggested. According to Leigh [13], "survivorship" is not just about the mere existence of life, but also about how well people survive, and hopefully thrive. Some advocates have therefore suggested terms such as "thrivers" and "someone who has had cancer." Currently, there is no consensus beyond the term cancer survivor. Nonetheless, it is important to recognize that not everyone wishes to be called a cancer survivor, and some reject the notion that they are different from anyone else.

Advances in cancer care have meant that the completion of treatment and beginning of survivorship has also become less defined for some patients. Surgery, chemotherapy, and radiotherapy may extend over many months. Emerging treatments such as immunotherapy can extend treatment even further. Consequently, the concept of survivorship has also shifted over time.

Cancer is actually a collection of more than 100 distinct diseases with radically different effects, treatments, and outcomes, so it is important to bear in mind that each experience will be different. Some experience few late effects of their cancer and its treatment, while others experience permanent and disabling symptoms that impair their ability to go about daily life. Although it may not be possible to predict the psychological sequelae for each patient, it is important to be aware of the common patterns of psychological issues facing this population so that appropriate care can be offered.

The Importance of Attention to Psychosocial Care in Cancer Survivorship

The psychological issues faced by cancer survivors do not just disappear over time and can be long-lasting without intervention, leading to adverse impacts on health-related quality of life, and low adherence to follow-up guidelines. The National

Cancer Control Network Survivorship Guidelines [5] clearly state that care of the cancer survivor should include assessment of late psychosocial and physical effects and interventions for consequences of cancer and treatment (including medical problems, symptoms, psychological distress, financial, and social concerns).

Despite these recommendations, there is evidence that over half of cancer survivors do not have a discussion with their treating clinician about the psychosocial effects of cancer [14]. This may be because attention to psychosocial issues is not seen as central to the scope of practice for busy clinicians whose primary focus is typically biomedical. Lack of confidence about addressing psychosocial concerns can be another barrier, and this is compounded because of the complexity of psychosocial needs of many cancer survivors which leads to uncertainty about how to respond, especially if there are not clearly defined referral paths for specialized psychosocial care [15].

In general, it is appropriate to adopt a stepped-care approach to psychosocial care for cancer survivors [16]. In such a model all patients are seen as potentially benefitting from information and relatively few patients will require more specialized care. Stepped care is self-correcting in that the outcomes of interventions are monitored routinely, and care is "stepped up" to the next level if current interventions are not achieving significant health gain. The stepped-care model involves regular assessment of psychological distress at clinically significant timepoints for each patient, with triage to one of five steps:

- Step 1: provision of information and self-management advice for all patients;
- Step 2: delivery of supportive care and psychoeducation for those with mild-moderate levels of psychological distress;
- Step 3: counseling with psychoeducation for those with moderate levels of psychological distress;
- Step 4: care delivered by psychosocial specialists for those with moderate-severe levels of psychological distress;
- Step 5: rapid review for those with severe distress (such as suicidal ideation) typically with a psychiatrist.

All cancer clinicians are well-placed to inform patients about potential medical and psychosocial late effects, including sexual dysfunction, pain and fatigue, psychological distress, and concerns related to employment and insurance. Although these discussions should take place once a treatment plan is formulated and be repeated along the cancer trajectory [11, 17], they assume particular salience for patients once active treatment is completed. A better understanding can help patients feel confident about their ability to deal with survivorship-related issues and to take charge of their own follow-up.

Many patients report acting "on autopilot" in order to survive during their cancer treatment and it is only after completion of treatment that they reflect more broadly about the impact of cancer on their health overall, and social and occupational roles. As a first step empathic acknowledgment of the cancer experience and the need to adjust to different circumstances is important. Clinician empathy is associated with higher patient satisfaction, better psychosocial adjustment, and less psychological distress [18]. In addition, provision of high-quality information is of central

importance and prospective studies have found a positive relationship between clinicians' provision of survivorship information and mental and global health-related quality of life, and a negative relationship between information provision and depression and anxiety [19]. This is an opportune time to reinforce recommendations about high-quality sources of information. There is also an opportunity to identify misperceptions. Clinicians can assure patients that discussing their feelings will not adversely influence their prognosis and that they do not have to adopt the "brave warrior" stance so commonly advocated in the media as there is no consistent evidence that stress or "negative thoughts" cause cancer or affect prognosis [20]. Having access to peer networks for emotional and social support is a priority for many cancer survivors and clinicians can provide information about support services available and how these can be accessed.

The impact of cancer extends beyond the patient to their family members and the needs of partners, spouses, children, and other loved ones all need to be considered [11], particularly those who take on the role of caregiver. Clinicians should include the family or caregiver during consultations when possible and acceptable to the patient, inquire about how they are coping and feeling, and address the needs presented during consultations [17]. Unique concerns can arise for some patient groups and their carers. For example, immunotherapy for advanced melanoma has resulted in dramatic clinical responses; however, the treatment is ongoing, and carers may face increased distress and burden not only because of uncertainty about the future but also because of side effects experienced by the patient. Fatigue may be prominent and affect the ability of the patient to engage in paid employment and social relationships meaning that carers must "step-up" to provide increased support which in turn affects their stamina. Apprehension and vigilance about identifying and reporting side effects can place carers in the role of an "unofficial health system" [21] meaning that identification of their psychosocial concerns is an important part of care. Another potential stressor for carers and family members is consideration of predictive genetic testing. As the availability of genetic testing becomes more widely known, it will be increasingly important for oncology clinicians to be familiar with the psychosocial costs and benefits of such testing, ensuring family members considering predictive genetic testing are referred so that they are sufficiently informed, prepared, and supported [22].

Foundation Strategies to Enhance the Psychosocial Well-being of Cancer Survivors

Effective communication and responsiveness to patients' emotional cues is essential to survivorship care in a patient-centered approach. In fact, the importance of communication in oncology practice is so critical that many guidelines list effective communication as part of the curricula and continued professional development of all clinicians in the delivery of patient-centered care [17]. Patients reporting good communication with their clinician are more likely to be satisfied with their care, adhere to prescribed treatment, and follow preventative health advice [23].

Lack of time is a commonly cited barrier to communication especially about psychosocial issues. However, the medical literature provides evidence that the use of patient-centered communication does not take more time. In fact, studies have found no differences in consultation time, even when clinicians asked and responded to more questions [24]. Therefore, it is not the actual time spent with the patient that helps their psychosocial adjustment, but rather what happens during that time. The following key elements of good communication are some basic communication techniques that can enhance the detection of patients' emotional concerns, and these can be applied even in the briefest of clinical encounters.

Key Elements of Good Communication

Good Eye Contact

Nonverbal communication may convey more information than verbal behavior in a clinical encounter and patients are often highly sensitive to the nonverbal behaviors of clinicians [25]. Eye contact is an important nonverbal behavior and essential for fostering confidence in the clinician. Good eye contact conveys a message of genuine care and interest and instills a feeling of comfort in the patient. Absence of eye contact on the other hand can be interpreted as lack of interest. Rather than feeling reassured and encouraged to talk about their concerns, this can leave the patient feeling unsupported or even abandoned. However, it is important to be aware of cultural considerations regarding eye contact.

Acknowledgment and Clarification

Not all patients find it easy to reveal their emotional concerns during consultations. In fact, less than one-quarter of patients actually do so [26]. Patients may keep emotional difficulties to themselves because they regard them as an inevitable consequence of cancer or worry they will be perceived as "ungrateful" by their clinician. Patients often believe that clinicians have too little time so do not want to complain or burden them further. This can especially be the case in survivorship care when the patient has come to like and respect their clinician over a long period of time. Another common reason that patients do not discuss their concerns is the perception that clinicians are not interested in their personal experiences [27].

The following techniques are likely to be helpful in acknowledging and clarifying a patient's concerns:

- *Making empathic statements*: there is evidence that simple empathic statements can help people cope with their distress [28]. For example, when responding to emotional cues of anxiety or distress, comments such as "You've had a challenging time" or "I can imagine this has been very distressing for you" indicate interest and recognition of the patient's concerns.
- *Use of open questions*: Open questions allow patients to express themselves, while closed questions permit only a "yes" or "no" response and can inhibit effective communication. For example, in talking with patients in a follow-up

consultation asking "How would you say the treatment has affected you?" or "How have you been feeling since finishing treatment?" are likely to elicit a detailed and meaningful response, compared with a closed question such as "Are you coping OK?"

- *Clarifying psychological aspects*: Questions with a psychological focus can help elicit patients' emotional concerns. This includes asking patients direct questions about how they are adjusting psychologically: "It sounds like you have been worrying a lot about what this cancer will mean for your future. Can you tell me more about that?" Or: "You've told me the pain is still there. How has this been affecting you emotionally?" This can be followed by some questions about the situation at home. This signals to the patient that attending to his or her concerns is an important and usual part of cancer care.

Summarizing

Summarizing is an often under-acknowledged skill. Summarizing does not mean to merely "summarize" what the patient has said. Rather, it is a key strategy that conveys to the patient that the clinician has fully understood their current social situation, their worries, and thoughts about the future. Summarizing the patient's priorities and main concerns therefore require active listening to what the patient is communicating. It also allows them to express another important piece of information that may have been missed or identify anything which may have been misinterpreted. For example, after meeting to discuss a survivorship care plan the clinician could say: "Let me check that I've understood everything you've told me. It's been just over a year since finishing treatment. You've had to spend a lot of time in isolation which made it difficult to connect with other people and this really knocked your confidence. Returning to work full-time was initially impossible to consider but just recently you have gone back to working part-time. This has been a big milestone for you and has allowed you to build up your confidence again. However, the transition back to work hasn't been without difficulty. Concentration and tiredness are two main factors that you struggle with." The patient might say, "Yes, that's right," or bring up another important piece of information such as "Yes, that's right, and I worry about what would happen if the cancer came back and whether I'd be able to work at all."

Provision of Information

There are evidence-based recommendations for giving information and checking understanding [17, 29]. Overarching principles include:

- Providing information in clear, specific, and simple terms, without the use of medical jargon
- Giving the most important information first
- Actively checking for understanding and encouraging questions (e.g., "I just want to check that I have given all of the relevant information. Can you please explain to me what you understand about what we've just discussed? Then I can fill in any gaps")

Although the clinician may see the provision of information as a discrete event, it is likely that information will need to be repeated over time, as the amount and type of information desired may change over time depending on changes in disease status, emergence of new symptoms, and changes in social circumstances.

Specific Issues Which Merit Detailed Attention and More Specialized Care

The foundation strategies described above are important for all consultations. There may be particular issues which require more focused exploration and in some instances, it may be necessary to offer referral for specialized psychosocial care. The following is not exclusive but covers commonly encountered issues.

Recognition of Social and Cultural Sensitivities

Sensitivity to the particular needs of each individual is important, with an awareness of social and cultural factors that influence patient attitudes and beliefs. Social and cultural sensitivity involves more than a mere assessment of whether a person speaks English or not; it requires a willingness to understand differences in attitudes and beliefs that are sometimes based on family background and experiences and sometimes based on culture and language. In this context, the question "Where do you come from?" is unhelpful, inappropriate, and insensitive. Assumptions should not be made about a person's language based on visible appearance. A better question to ask a patient would be "What do I need to know about your culture and beliefs in order for me to take the best possible care of you?" The ability of clinicians to sensitively ask patients about any social or cultural influences in their survivorship journey lies at the core of effective communication and optimal psychosocial care.

In many services, clinicians are treating patients whose English proficiency is low. Many services will provide access to interpreters who should be used in the first instance as untrained interpreters are more likely to make errors, violate confidentiality, and increase the risk of poor outcomes. "Untrained" health professionals may contribute to communication challenges too as few have received formal training in ways to maximize the benefit of working with an interpreter. Specific recommendations are:

1. Meet with the interpreter before the interview to give some background, build rapport, and set goals. A trained interpreter can assist clinicians to understand cultural beliefs about illness
2. Speak directly to the patient, not the interpreter
3. Use first person statements rather than "tell her"
4. Insist on sentence by sentence interpretation
5. Use "teach-back" to check for comprehension rather than asking "do you understand?" which will likely attract an affirmative response even if that is not the

case. In the teach-back technique, the patient is asked to repeat what they have been told "So I can check if I've been clear" [30]

Even if language proficiency appears to be adequate, the person may still struggle to fully understand the information provided. Health literacy has been defined as "the degree to which individuals can obtain, process, and understand the basic health information and services they need to make appropriate health decisions" [31]. In Europe, it is suggested that 47% of the population have insufficient or problematic literacy, although this varies across countries [32]. Subgroups with higher proportions of limited health literacy are those with financial deprivation, low social status, low education, and old age. Medical education typically pays little attention to health literacy. The Plain Language Thesaurus for Health Communication is a valuable resource to assist clinicians in their communication with patients [33].

Depression and Anxiety

The prevalence of mood disorders in cancer survivors is estimated to be 20% although this varies depending on the population and cancer type [34]. Identification and treatment of depression and anxiety are critical as these conditions undermine the ability of the individual to cope with residual symptoms [35], reduce adherence to treatment recommendations [36], and are associated with more than doubling of readmission rates [37]. The development of depression and anxiety may be considered as a "final common pathway." However, many patients do not come to the diagnosis with a "clean slate" and background social concerns and a past history of psychological issues are risk factors for the development of depression and anxiety in the context of cancer. Further factors which may contribute are the circumstances of the diagnosis (for example, a perception of delay), the nature and prognosis of cancer, and toxicities and side effects related to treatment (such as lymphoedema) [38].

It is recommended that patients treated for cancer be routinely screened for depression and anxiety using a validated measure across a range of time points including when there are changes in disease status and transitions such as completion of a defined treatment protocol [39]. Many such measures pose a respondent burden, there may be costs associated with their use, and stigma may limit the willingness of patients to complete them. The Distress Thermometer devised by the National Comprehensive Cancer Network (NCCN) may be a useful initial screening tool, as the word "distress" is seen as non-stigmatizing. Patients rate their distress on a linear scale of 0–10 and complete an accompanying problem list. A score of 5 or greater should trigger further questions and assessment [5]. For this purpose the PHQ-9 is recommended, which is free to download, poses a low respondent burden, and is quick and easy to score. A score of 10 on the PHQ-9 represents the cut-off for moderate depression [40]. Determining that the person may be depressed should trigger further discussion. Many of those offered referral for psychological treatment will decline because of stigma (including apprehension about medication)

and the perceived burden of travel and parking to attend a clinic [41]. However, there is compelling evidence of the effectiveness of individual interventions [42] and antidepressant medication when required [43].

It is recommended that health professionals broach discussion about psychosocial concerns as mainstream and attest to the potential benefit of interventions: "We need to care for you as a person, not just focus on the cancer. Your emotional well-being matters just as much as your physical well-being" and "Depression and anxiety are very common after a cancer diagnosis. The good news is that treatments are usually very effective—and they do not necessarily mean you would need to take medication."

Treatment of Depression

Treatment of depression and anxiety should be tailored to the individual and incorporate attention to specific factors which may have contributed (for example, pain, fatigue, and social isolation). For mild cases, basic strategies focus on restoration of pleasurable activities, attention to sleep and exercise, correction of misinformation, and maximizing social support (which may include referral to a support group). Relaxation training and meditation can assist. Individual therapy has demonstrated benefit [42] and may include treatments such as Cognitive Behavior Therapy (CBT). In CBT the person works on the identification of unhelpful thoughts (for example, "My friend didn't call when she said she would. I know everyone is fed up with me") and is assisted to challenge these thoughts (for example, "What other explanation is possible? What else is going on in your friend's life that might have distracted them? Have you always had your phone charged?"). More severe depression may require antidepressant medication, typically a Selective Serotonin Reuptake Inhibitor (SSRI), taking into account the potential for drug interactions [5]. Of note, paroxetine use in women treated with tamoxifen is associated with an increased risk of death, postulated to be due to the reduction of the benefit of tamoxifen by paroxetine [44]. Clinicians have a powerful role in informing patients of the robust evidence of potential benefits of antidepressant medication [43], taking into account specific contraindications.

Managing Anxiety

While some degree of anxiety when faced with a cancer diagnosis is normal, high anxiety can lead to diminished ability to make decisions and plan for the future. Cancer survivors with high anxiety can feel powerless to make changes and adapt. Anxiety disorders typically have their onset in adolescence or early adulthood, and anxiety in cancer survivors may represent an exacerbation of a preexisting condition hence the person may have long-standing attitudes and concerns about their health and the future.

Treatment of anxiety should be tailored to the individual after exclusion of a medical cause for symptoms (for example, hyperthyroidism). The cornerstone is education and attention to lifestyle issues and comorbidities (such as alcohol use). Initial treatment should be CBT which has a long-established evidence-base. There is emerging evidence of the effectiveness of digital CBT [44]. Medication can be

used if symptoms are severe or there is an insufficient response to CBT. First-line treatment is Selective Serotonin Reuptake Inhibitors, but they should be commenced at a lower dose than normal as people with anxiety are more sensitive to initial side effects which can include sleep disturbance, gastrointestinal upset, and exacerbation of anxiety. Benzodiazepines have no role as a primary treatment for anxiety because of the risk of tolerance and dependence [45].

Fear of Cancer Recurrence

Arguably one of the most common but insufficiently addressed survivorship issues is fear of cancer recurrence. Fear of cancer recurrence (FCR) has been defined as "Fear, worry or concern relating to the possibility that cancer will come back or progress" [46]. Almost half of the cancer survivors report moderate to high levels of FCR and this figure approaches 70% in some groups (such as young breast cancer survivors), and for 7% this fear is severe and disabling [47–49].

FCR is an important issue to address in cancer survivors as it is associated with depression and reduced quality of life [50]. FCR does not necessarily equate with actual risk, and of particular concern, it does not appear to abate over time [47]. FCR may be identified when patients express concerns in consultations but may also be indirectly inferred in patients who ask repeatedly for reassurance or seek frequent unscheduled appointments or request nonstandard tests.

Given its prevalence, it is appropriate to routinely ask patients about FCR. Acknowledgment that some degree of anxiety is normal after cancer treatment, followed by exploratory questions can initiate discussion, for example, "Most people who have been treated for cancer say it is life-changing. Some tell me that it has a big impact on how they feel about themselves and their future." "How would you say things are going for you?" Clarification can include questions about worry relating to cancer coming back, how often this happens (e.g., from time to time or every day and most of the day) and how they respond (e.g., checking their breasts multiple times per day, scanning the Internet for information, or conversely avoiding follow-up appointments "in case I get bad news"). Asking about the impact on work and relationships can be helpful. Those with high FCR may report that they feel "stuck" and that they are finding it hard to make plans—"I know it will come back so what's the point?"

Clinicians can assist in several ways:

1. listening and validating that some degree of anxiety is normal
2. providing information about prognosis and evidence-based guidelines for follow-up
3. recommending credible information sources which are aligned with the patient's literacy level
4. advising on ways to reduce risks such as achieving a healthy weight and active lifestyle
5. avoiding conducting investigations unless clinically indicated (that is, not conducting extra tests "to be sure").

The desire to reassure someone who is worried is powerful however in those with high FCR it is more helpful to first listen and acknowledge their concerns. Determining the severity of FCR and the need for specialist treatment is more complex. Recently a single-item screen has been developed for this purpose. The researchers suggest that a score of 45 on the question: "On a scale from 0 to 100, what is your subjective level of fear of cancer recurrence at this time?" would identify the majority of those with high FCR [51]. A variety of interventions based on a range of theoretical underpinnings have demonstrated effectiveness in reducing FCR with improvement largely maintained at follow-up [52]. Referral to a psycho-oncology professional can be considered or if this is not available, referral to a support group or online intervention may be appropriate [53].

Sexuality and Body Image

Sexuality is an important part of well-being and is of particular importance in oncology, as virtually all cancer treatments have some impact on it. Although prevalence rates for sexual difficulties associated with cancer and its treatment vary depending on the diagnosis studied, treatment type, and how and when sexual function is defined, estimates are reported to range from 40 to 100% [54]. People with cancer often report body image disturbances that impact self-esteem and sexuality, including pain (largely in women), erectile dysfunction (in men), fatigue, and visible changes such as disfigurement, scarring, weight changes, and hair loss [55, 56]. Many women experience life-changing but unseen effects of systematic treatments, including treatment-induced menopause and permanent infertility. Patients may also experience changed priorities within or external to their relationship, or psychological distress including fear, anxiety, and depression that may lead to changes in sexual interest and strain on relationships. If left unaddressed, these issues can lead to long-term psychological concerns among cancer survivors.

Normalizing these issues may help patients reach a new comfort level with body image and sexual functioning following their cancer treatment and facilitate the expression of concerns. However, sexuality is considered a sensitive topic and patients may feel uncomfortable or embarrassed to raise the topic. Finding ways to ask about sexual health concerns during routine follow-up care is important. The conversation could include the patient's partner, only if the patient so wishes and should take into account cultural/religious beliefs, and sexual orientation [54]. Cancer Australia has a practical resource to assist clinicians to initiate discussion [57]. Although developed to address issues for women treated for breast cancer, many of the questions can be readily adapted to other patient populations:

1. "Many people find that treatment for cancer affects their self-esteem or changes their interest in sex—this is common, and it can have a big impact on your life. Is this something you would like to talk about?"
2. "Many people experience side effects as a result of their treatment that impact relationships or sexual activities, such as pain, worry or fatigue. Do you feel like these or any other symptoms are affecting your sex life or relationship? What do you (and your partner) find most concerning?"

Clinicians can guide patients to high-quality evidence-based resources. The American Cancer Society (www.cancer.org) and the National Cancer Institute (www.cancer.gov) both have comprehensive patient informational booklets about sexuality after cancer. There are few psychological interventions specifically designed to address body image concerns and sexual communication. Among interventions evaluated, most have been tested in breast cancer survivors and incorporate psychoeducation, cognitive behavioral therapy, or mindfulness and are directed at the individual or couple, or delivered in a group [58]. For those with persistent concerns and/or distress, psychological counseling can be considered and can be provided by a specialized therapist (e.g., sex therapist) or a psycho-oncology professional.

Cognitive Changes

Post-chemotherapy cognitive Impairment, often termed "chemobrain" is recognized as a problem in a subgroup of patients treated for cancer, although the precise mechanism is still not fully elucidated [59]. Typical problems are memory, concentration, information processing, and executive function. Executive function includes self-awareness and self-regulation, mental flexibility, planning, and problem-solving. Impairment in executive function may be largely invisible to others but can exert a profound impact on daily functioning as the person finds it difficult to "multi-task" and process information quickly. Self-perception of cognitive problems does not always neatly align with neuropsychological testing results, highlighting the need for research into standardized self-report measures [60].

There is emerging research suggesting the effectiveness of cognitive rehabilitation programs. One such program "Insight" from Posit Science is a computerized neurocognitive learning program based on the neuroplasticity model. It includes tailored exercise in the domains of visual precision, divided attention, working memory, and visual processing field [61]. In a RCT of 242 participants, the intervention group demonstrated significantly less perceived cognitive impairment than the control group [60].

Key practice points are acknowledgment of subjective concern about "chemobrain" and exclusion of contributory problems such as depression or endocrine disorders such as hypothyroidism. Attention to lifestyle factors such as diet and exercise and limiting use of alcohol will not improve cognitive function per se but may improve adjustment. Clinicians can advise on practical strategies to enhance adjustment:

1. encouraging the use of a notebook (for example, to record phone discussion)
2. keeping a structured diary
3. undertaking challenging tasks earlier in the day when less fatigued
4. reducing external distractions such as music when undertaking complex tasks
5. repeating a person's name when introduced to someone
6. keeping objects (such as car keys) in the same place

7. encouraging the person to increase their focus on a particular task through verbal reminders (for example, the person saying out loud: "Mary, this is important. You need to focus")

Financial Toxicity

The financial burden of cancer can be substantial for patients and their families, even for those who have access to universal healthcare systems or health insurance [62]. More recently, experts have asserted that the financial "pain" of undergoing cancer treatment should be considered analogous to physical treatment toxicities such as neutropenia, vomiting, insomnia, or depression that lead to poorer patient outcomes, or delayed/discontinued cancer care [2]. Increasingly, this has led to the use of the term "financial toxicity" to describe the financial hardship or distress that may be a side effect of cancer treatment. Financial toxicity is not simply a feature of the acute treatment phase but has been shown to continue up to 10 years after diagnosis [63]. Financial toxicity may be particularly severe for (1) families of children with cancer who give up work to care for a child with cancer, (2) patients from rural and regional areas who must travel to access care, and (3) younger cancer patients with few financial reserves [2, 64].

Financial toxicity is an important issue to address in cancer survivorship care as psychosocial well-being and financial health are intimately related. Nearly half of cancer survivors report financial toxicity [2], and this is associated with at least a threefold increased risk of anxiety and depression [64]. The American Society for Clinical Oncology states that "communication with patients about the costs of care is a key component of high quality care" [65]. In the first instance, preparing patients and their families for the potential financial effects that could have an ongoing impact at the completion of treatment is vital. This allows patients and their families to make fully informed decisions about their care. Secondly, given the significant financial risk many patients face, an opportunity to raise concerns should be offered to all patients. Acknowledging the financial burden of cancer and actively inviting patients to talk about any financial concerns they may have is likely to be of benefit. For example, "Some patients tell me they have trouble paying for their prescriptions or paying gaps for medical treatments or visits, has this been an issue for you?" This conveys acceptance and encourages the expression of financial concerns. Furthermore, validated screening tools such as the 11-item COST-FACIT [66] may assist with identifying those patients at high risk who may benefit from referral to support services.

Returning to Work

A large proportion of patients will be part of the workforce at the time of diagnosis. For this group, return-to-work is an important aspect of social reintegration and a positive step toward an improved quality of life. Unfortunately, the journey back to

work is rarely simple for those who are dealing with the impact of cancer and cancer treatment. Besides physical and functional disabilities, increasing psychological distress and mental disorders can adversely affect a patient's work ability, work conditions, and work satisfaction. These effects can make it challenging for patients not only to return but also remain at work. Between 26 and 53% of cancer survivors lose their job, or quit working over a 6-year period following their diagnosis [67]. Survivors of cancer have reported obstacles in the workplace including dismissal, failure to hire, demotion, denial of expected promotion, and hostility [68]. Consequently, the identification of work-related problems should be an important treatment goal for every clinician.

Most survivors want to discuss the impact of their cancer on their participation in working life with their clinician [68]. Clinicians are usually a survivor's first and most influential source of information. Thus, although clinicians cannot be expected to be experts in this area, they should be aware of survivor's needs and rights and guide them to credible resources that provide more information and assistance. A small, but effective number of psycho-educational interventions have led to higher return-to-work rates than care as usual and can be utilized by clinicians in combination with physical training and vocational elements [69]. Clinicians can assist by:

1. having an open discussion with patients about their expectations and concerns about returning to work.
2. drawing up a specific and gradual return-to-work plan in collaboration with the patient, occupational health professional, and the employer.
3. evaluating if the demands of work align with the patient's capabilities, taking into account their psychological well-being, cognitive functioning, and attitudes about work. Discrepancies could mean that the demands are too high, leading to heightened distress. These issues can subsequently be addressed by referring patients to a support service according to their needs, such as physical, occupational, or psychological support services.
4. asking patients if they have experienced any challenges in returning to work. Providing a written letter to employers explaining a patient's abilities and limitations at work in a way that may dispel myths about their current and future capabilities [68].

Existential Issues

The diagnosis of cancer poses a challenge to the sense of self of the individual, their optimism and certainty about life. It is common for the individual to state that cancer has made them rethink their attitude toward relationships, work, and their purpose in the world. Some see the diagnosis as an opportunity for personal growth which gives the impetus to initiate positive change in their life. Conversely, others may experience distress as they reflect more critically on their life and achievements to date, leading to feelings of demoralization in which they lose focus and optimism. Although perhaps understandable in those facing advanced disease, these

feelings can also occur in those with good prognosis and lead to the person feeling "stuck" and unable to move forward.

These existential concerns do not constitute disorder but still affect the person's life and relationships. There is a body of evidence suggesting that psychosocial interventions can be of benefit [70]. Even apparently simple discussions can help the person who is struggling with existential issues. Examples include asking about who are their sources of support, how they make sense of their situation, and reflecting on past strengths in dealing with adversity [71]. As new therapies emerge with the promise of extended survival, it is important to recognize that these can also pose an existential challenge. Particularly for patients with metastatic melanoma there may be uncertainty about sustained benefits of treatment and disease trajectory, the risk of emergence of toxicity and strain about future treatment decision-making [72]. Providing an opportunity for individuals to discuss these concerns is likely to be of benefit. Health professionals may be tempted to offer reassurance however in the first instance listening and validation of distress are vital.

Emerging Concepts in Survivorship Care

As the population of cancer survivors continues to grow in volume, oncology specialists are placed under increasing pressure and workload. Care models that are oncology-led and focused on surveillance for cancer recurrence can leave survivors with significant unmet needs. At the same time, these models are not sustainable, and they may not represent the best use of oncology specialist expertise.

Strengthening Collaboration Between Oncology Specialists and Primary Care Providers

Most people meet the oncologist for the first time with a cancer diagnosis. In many instances, patients will have preexisting relationships with primary care providers which extend over many years. Returning to them for follow-up is viewed as an acceptable alternative by patients and research suggests that disease and quality of life outcomes are similar to follow-up care conducted by oncology specialists [73, 74]. An Australian survey found that oncology specialists felt that too much of their time was spent on follow-up care, taking away their time from newly diagnosed patients requiring their expertise [75]. Hence, survivorship care models must be designed to be both acceptable to patients and feasible for oncologists. The seminal Institute of Medicine report "From cancer patient to cancer survivor, Lost in Transition" [11] suggests that ideal survivorship care should comprise shared follow-up responsibility between oncology specialists and primary care providers.

Primary care providers are well-placed to provide comprehensive care oversight. They can safely and effectively monitor symptoms and treatments, support the management of psychosocial care, promote and motivate health-behavior change, and facilitate timely and appropriate access to specialist oncology care. Primary care

providers favor a shared-care model, in which they share follow-up responsibility with the oncologist and feel that they can deliver this care with appropriate support and referral pathways [73]. Delegating and sharing follow-up responsibility can free oncology specialists to see new and more serious cases that can most benefit from oncology expert face-to-face contact. This model of survivorship care has been successfully implemented in the follow-up of women with breast cancer, with findings showing strong support for greater primary care provider involvement in follow-up cancer care [76]. Through close communication and collaboration with primary care physicians, oncologists can have an important effect on the long-term health of cancer survivors and ensure patients receive care that is coordinated, with a clear and seamless journey between specialist and primary care settings.

Recognizing and Responding to the Needs of Carers

Good, reliable caregiver support is crucial to the physical and emotional well-being of patients throughout the trajectory of their cancer experience. Although there is evidence that family members find personal satisfaction and accomplishment in providing a quality of life to a loved one, it can also be a frustrating or even overwhelming experience for family members [77]. Giving care and support can be hard to maintain during the survivorship phase, and can take a toll on the health and well-being of family members. Caregivers continue to spend a substantial amount of time providing medical, emotional, instrumental, and other tangible support during the survivorship phase, with an average of 8.3 h per day spent providing care in the 2 years after diagnosis [78]. This can lead to increasing stress over time, and deplete family caregivers physically, psychologically, socially, and even financially. Family caregivers of long-term cancer survivors can often have mood disorders that hamper their quality of life. A meta-analysis of 43 studies investigating mood disorders in spouses of long-term cancer survivors reported that the prevalence of anxiety was 40% and that of depression was 26%, even though the mean time since diagnosis was approximately 7 years [79]. In some cases, the psychological burden for the caregiver may exceed that of the patient. Positive associations have been reported between patient and carer psychological distress [80], which suggests that a caregiver's distress directly impacts a patient's well-being and vice versa.

Along with an awareness of patients' emotional needs, it is important to recognize the impact of caregiving on family members and incorporate questions about their adjustment. Given the prevalence of mood disorders among caregivers, it is appropriate to ask caregivers about the impact on their own emotional well-being. For example, "Some caregivers tell me that they find it difficult to juggle caregiving responsibilities with their other day-to-day responsibilities and that this can put them under a lot of strain. How are things going for you?" These simple questions express support and can encourage caregivers to voice their worries. A variety of interventions delivered jointly to patients and caregivers or caregivers alone have demonstrated effectiveness in reducing caregiver burden and improving self-efficacy and can be incorporated into routine follow-up care [81]. For caregivers displaying

high levels of psychological distress, referral to a specialist in psycho-oncology can be considered. There are also many resources and community-based support services available to caregivers of patients at no charge. The American Cancer Society (www.cancer.org) and the Australian Cancer Survivorship Centre (www.petermac.org) both have comprehensive online information booklets and videos about caring for someone with cancer. In addition, including caregivers in survivorship care planning is likely to be helpful in preparing caregivers for the care tasks that will be needed during the survivorship phase.

It is important to consider those other than spouses of the patient who may take on carer responsibilities, such as children, parents, siblings, or friends. As the population continues to age, a growing number of adult children will find themselves in the position of having to provide care to older adults. Timely attention to this subgroup of caregivers is important as they juggle other social roles while providing care to a family member with cancer.

Survivorship Care Plans

Survivorship care plans (SCPs) are increasingly being advocated as a tool to improve outcomes for cancer survivors. SCPs are formal, written documents which document the person's diagnosis, treatment, and potential long-term and late effects, along with recommendations for follow-up and strategies to remain well including lifestyle changes [82]. Internationally, SCPs are promoted as a means of assisting clinicians to be actively engaged in attending to survivorship issues and engaging primary care providers in their enactment [83].

While survivorship care plans have intuitive appeal, a recent review of survivorship care plans for a range of cancers found insufficient evidence of benefit on long-term health outcomes [84]. The reasons for lack of long-term impact may relate to the SCP itself. Although there may be variation in their development and health professionals involved, commonly they are based on a single consultation. The person who receives the SCP may fail to enact aspects of the plan—in a study of a SCP for patients treated for head and neck cancer most participants failed to review the plan or act on recommendations, and none collaborated with their primary care physician to actualize the plan for lifestyle changes despite this being a clear recommendation of the SCP [85]. This is consistent with the work of Birken et al. [86] which demonstrated the critical role of local champions and systems to enact SCPs. Another critical issue is clarity about the precise components of the survivorship care plan. For example, in the ROGY trial, patients with gynecological cancer who received a survivorship care plan experienced greater concerns and worse social functioning than controls [87]. This care plan comprised information on the most common and long-term effects of treatment, signs of recurrence and secondary tumors as well as information on rehabilitation. The authors contend that details about recurrence and progression may have heightened illness perception.

Overall it is reasonable to consider that a survivorship care plan is one component of survivorship care, rather than a "stand-alone" intervention. Enhanced

benefits are likely to be seen when they are seen as a dynamic document to facilitate ongoing discussion and focused action which incorporates the role of community-based health professionals [83].

The Emotional Impact for Clinicians Working with Cancer Survivors

Stress and burnout are commonly used terms and medical practitioners are considered to demonstrate higher rates of burnout than workers in other fields [88]. The obvious contributors to work-related stress for oncologists include workload, frequency of giving bad news, and the deaths of patients. "Compassion fatigue" is also cited as a contributor—when the practitioner fails to take steps to replenish their personal needs despite the demands for compassionate caring for patients [89].

Caring for cancer survivors may at first glance seem a role less likely to cause emotional distress as these patients are by definition surviving. However, responding to complex residual symptoms and side effects of treatment can be challenging, especially as this is underpinned by vigilance about detecting recurrent disease and late effects. Oncologists may find it challenging when caring for patients with whom they identify, for example, because of age, cultural or social background [90]. In addition, responding to patients with anxiety or depression can be challenging particularly if the oncologist does not feel confident about responding to these issues. Strategies which are likely to help include being part of a multidisciplinary team in which challenging cases can be discussed and having defined pathways for referral of patients whose psychosocial needs mean that they require specialized care. Challenging prevailing attitudes about working to the point of exhaustion requires a shift in health systems which can advocate for "attraction to wellness" rather than a solution for burnout [91].

Key Messages

- One in two cancer survivors experiences significant levels of psychosocial distress.
- High levels of distress can lead to more serious psychological problems and are associated with a reduction in quality of life, increased healthcare service use, poor adherence to follow-up recommendations, and shorter survival.
- It is recommended that psychosocial needs be regularly assessed using the best possible evidence and coordinated, integrated care.
- Good communication is important in helping patients live well after cancer. Key strategies include good eye contact, acknowledging and clarifying the patient's concerns by making simple empathic statements, use of open questions with a psychological focus, and summarizing the patient's priorities and main concerns.
- Sensitivity to the social and cultural factors that influence patient attitudes and beliefs is required.
- It is recommended that cancer survivors be routinely screened for depression and anxiety using a validated measure across a range of time points including when

there are changes in disease status and transitions such as completion of a defined treatment protocol.

- Fear, worry, or concern about the possibility that cancer will come back or progress is one of the most common concerns for patients and effective interventions are available.
- Although an estimated 40–100% of cancer survivors report sexual difficulties and body image concerns, they are unlikely to raise the topic. Clinicians can help by initiating discussion about sexual health.
- Many patients experience cognitive changes after cancer treatment. Clinicians can advise on practical strategies to enhance adjustment, including aerobic exercise and cognitive training.
- Nearly half of cancer survivors report financial toxicity and this is associated with at least a threefold increased risk of anxiety and depression.
- Psychological distress can adversely affect a patient's work ability and satisfaction. Cancer survivors also experience obstacles in remaining at work, including dismissal, demotion, and hostility.
- The completion of treatment can make patients rethink their purpose in the world. For some, this can initiate positive change, while for others this may lead to feelings of demoralization in which they lose optimism about the future.
- To ensure survivors' needs are met, oncology specialists should consider shared-care models in which they work collaboratively with primary care providers.
- Along with an awareness of patients' emotional needs, it is important to recognize the impact of caregiving on family members and incorporate questions about their adjustment.
- Survivorship care plans are one component of survivorship care, rather than a "stand-alone" intervention.
- Being part of a multidisciplinary team in which challenging patient cases can be discussed and having defined pathways for referral of patients whose psychosocial needs require specialized care are strategies that are likely to be helpful for clinicians caring for cancer survivors.

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Nutrition in Survivorship Care

18

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Research on nutrition and cancer risk has been having a significant development in recent decades, supported by epidemiological studies showing differences in the incidence of tumors according to different dietary patterns and food habits [1].

In the last years, also the attention on the role of diet and physical activity in the health of cancer survivors has increased.

Cancer survivors usually face several long-term health and psychosocial consequences of their treatment, including cardiovascular complications, endocrine disorders, osteoporosis, cognitive deficits, complications as well as weight changes [2]. These consequences, combined with the morbidity and mortality associated with the disease itself and its potential for recurrence, make it obvious that there is a growing need for recommendations on lifestyle choices for this population.

However, few observational studies have reported associations between diet and cancer survival, which have been different in design and results, leading to a lack of definitive evidence.

Several guidelines have been published for cancer survivors to achieve a better prognosis and quality of life (QoL).

In 2007, the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) updated its previous extensive systematic review of the evidence linking food, nutrition, and related factors to cancer incidence. It also addressed cancer survivors and concluded that due to the lack of sufficient research evidence, they should be encouraged to follow the recommendations for primary cancer prevention [3].

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The WCRF/AICR has continuously updated scientific research and recommendations on cancer prevention and survivorship regarding nutrition and physical activity, and presented the last results in 2018 [4]. The conclusions of this report were based on the available meta-analysis and systematic reviews. All different types of epidemiological studies (from descriptive to prospective) were considered, giving importance to results confirmed by studies conducted with different methodologies and replicated in different settings. Precise criteria have been assessed for the allocation of the level of evidence: the type of study (the most relevant are prospective studies), the lack of heterogeneity between studies, good quality, presence of a dose-response relationship, and, finally, the biological plausibility of the association.

The criteria for grading evidence lead to five possible levels: "convincing," "probable," "limited/suggestive," "limited/no conclusion," and "unlikely." Only convincing and probable evidence was used to draw up the recommendations.

From the above report, it appeared that obesity is the main risk factor for the development of cancer and control body weight is the major recommendation for cancer prevention.

Body weight results from the "energy balance" between caloric intake and expenditure.

Excess adiposity can contribute to a procarcinogenic environment through several pathways involved in inflammation, oxidative stress, cell proliferation and angiogenesis, inhibition of apoptosis/cell death, and metastases [5].

Several clinical studies have shown that caloric restriction can inhibit the carcinogenic process through various mechanisms mainly linked to metabolic alterations [6, 7]. Based on the WCRF and International Agency for Cancer Research in Lyon (IARC) reports, there is strong evidence that overweight and obesity are associated with an increased risk of developing colorectal, endometrium, kidney, esophagus (adenocarcinoma), menopausal breast, liver, gallbladder, stomach (cardias), pancreas, ovary, thyroid, mouth, pharynx and larynx, meningioma, multiple myeloma, and prostate (advanced) cancer [4, 8, 9].

Also the American Cancer Society (ACS) released guidelines on nutrition and physical activity for cancer prevention and highlighted the importance of weight management, physical activity, and diet [10, 11].

In USA, approximately 10.9% of diagnosed cancer cases during 2014 among women and 4.8% of those among men were attributed to overweight or obesity [12].

In Europe, it has been estimated that around 3.2% of cancers in men and 8.6% in women are attributable to excess weight [13]. The WCRF has confirmed a convincing and likely level of evidence for overweight as a risk factor for cancer incidence [14].

In the UK, it has been estimated that 17% (but with an interval from 4 to 38%) of tumors would be preventable through the control of body weight. Taking into account all cancer types and not only those associated with overweight, the risk attributable falls to 5.5% (4.1% in men and 6.9% in women) [15].

In summary, the WCRF recommendations stress the following dietary advice:

- Eat a diet rich in vegetable foods (whole grains, vegetables, fruit, and beans); eat at least 400 g of vegetables and fruit and at least 30 g of fiber each day.
- Limit consumption of (1) processed foods high in fat, starches, or sugars ("fast foods"); (2) red meat to no more than 350–500 g cooked weight per week. Red meat refers to beef, veal, pork, lamb, mutton, horse, and goat. Consume very little processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation (cold cuts, sausages,); (3) alcoholic drinks (it is best not to drink alcohol); and (4) sugar-sweetened drinks.
- Do not use nutritional supplements for cancer prevention, including micronutrients at high doses, as they are not recommended and in some cases may be harmful. Nutritional needs should be satisfied just by dietary intake.

A recent French prospective study involving over 100,000 subjects showed that the consumption of sugar-sweetened drinks and fruit juice was associated with an increased risk of developing cancer, particularly breast cancer, while the association between artificially sweetened drinks and cancer risk has not been demonstrated [16].

As reported by the WCRF, there is sufficient scientific evidence to claim that the consumption of sugar-sweetened drinks is associated with weight gain. In particular, the increase in visceral adiposity could favor tumorigenesis [17].

In recent decades, the progress in early diagnosis and treatment of cancer has led to a continually increasing number of cancer survivors, which is associated with a corresponding growth in the need for effective posttreatment management programs. In 2018, 43.8 million people worldwide were living with a diagnosis of cancer [18].

Currently, there is still insufficient research evidence regarding the effects of diet, weight, and nutrition on the risk of cancer recurrence. The research in this area, unlike for primary prevention, is often inconclusive and the WCRF report remains the most authoritative source of evidence [19].

Prospective research and randomized clinical studies on the role of diet, nutrition, and physical activity in cancer survivors have typically a short duration and small sample sizes. Moreover, they focus on specific dietary aspects and do not reflect "real life" food habits. The evidence on adverse effects or benefits for specific nutrients is also limited for this reason.

Among solid tumors, breast cancer is the most commonly occurring cancer in women and the second most common cancer type overall (24.2% of the total cases in 2018) [18].

Several studies regarding cancer survivors with breast cancer are available, but there are no definitive conclusions on nutrition and cancer risk due to the heterogeneity of the disease and the different treatments carried out. Some studies have reported improved overall survival, but the evidence is still currently limited [20]. Other data suggest that obesity is a predictor of poor outcomes in breast cancer survivors [20]. The exact cause is unclear, but chronic inflammation associated with obesity could be involved, as it may enhance disease progression [5].

Notably, the impact of overweight and obesity on the risk of developing chronic diseases such as diabetes or cardiovascular disease could contribute to reduce overall survival in cancer patients. There is also evidence that overweight or obese women present some tumor characteristics (larger size, advanced stage) that can affect the outcome.

Finally, it has been suggested that overweight women can have a reduced treatment efficacy due to underdosing of chemotherapy [20].

On the other hand, overweight patients may have sufficient lean body mass to achieve effective resilience against the metabolic effects of cancer and its treatment. However, it should be considered that it is not always possible to distinguish between voluntary or involuntary weight loss. Sarcopenia and cachexia are late complications associated with negative clinical outcomes, so an apparent beneficial effect of overweight could simply reflect a lack of "hidden" pathology [21].

More than 90% of head and neck cancer survivors who underwent chemoradiotherapy experience one or more nutrition impact symptoms (NIS) in the months or years thereafter [22].

In a recent publication, the authors systematically reviewed existing scientific evidence related to NIS and their impact on nutritional and quality of life outcomes in posttreatment head and neck cancer survivors [23]. These patients experienced severe eating difficulties and distress caused by NIS, while clinical outcomes are still largely underexplored. Large-scale prospective cohort studies are needed to investigate the associations between QoL and survival in head and neck cancer survivors. It is imperative to identify as soon as possible the risk factors associated with QoL in this nutritionally vulnerable patient population and to provide supportive care services to minimize their negative consequences [23].

Colorectal cancer is the third most common cancer type worldwide. After colorectal cancer diagnosis, a healthy lifestyle consisting of regular physical activity and an appropriate diet may improve prognosis and clinical outcomes [24].

Physical activity, including aerobic exercise such as walking, has been proposed to cancer survivors during or straight after treatment, to achieve several beneficial effects, probably also through weight reduction, such as the attenuation of "fatigue" and symptoms severity, leading to improved QoL. However, the effect on "tumor-specific" survival is still not documented. Therefore, currently, it is not possible to conclude that dietary interventions can necessarily improve survival in long-term cancer survivors.

Some associations between overweight/obesity at diagnosis and longer survival in patients with other types of cancer (colon and lung) have been detected [4].

After active treatment or during chronic therapy (e.g., hormonal therapy for breast cancer), the WCRF suggests the recommendations for primary prevention: body weight control, an adequate diet possibly according to personalized nutritional counseling, and regular physical activity [4, 20].

In specific clinical situations, such as metabolic diseases, total gastrectomy and in pregnancy, the WCRF stresses that nutritional support is needed by specialized healthcare professionals.

It should be noted that nutritional recommendations for cancer patients warn about low-calorie diets (e.g., macrobiotics or fasting) in subjects undergoing active treatment because they can compromise protein intake and lead to a critical lean body mass loss, which is associated with increased morbidity and mortality [25]. In addition, systematic nutritional assessment by skilled healthcare professionals is recommended for all cancer patients since diagnosis and during treatment and follow-up [26, 27].

Cancer survivors are an ideal population to promote interventions aimed at adopting healthy lifestyles, especially through a multi-behavioral approach including dietary modifications. Indeed, knowledge on nutrition and weight control should be based on scientific evidence and provided in a timely manner. However, as explained above, there are limitations due to the heterogeneity of the population and the presence of numerous confounding factors (cancer types, disease stages, and associated treatments).

Research in this area is still in its early stages. In the future, intervention studies are warranted, in order to identify the best nutritional strategies based on adequate molecular and metabolic predictors, which would allow the customization of weight loss regimes in terms of doses and optimal distribution of macronutrients. This would allow cancer survivors with different types of cancer to recover or maintain an adequate nutritional status and body composition and to achieve the best possible QoL. A well-designed nutritional intervention trial requires a broad representation by cancer type, age, gender, and ethnicity, as well as sufficient sample sizes to conduct reliable subgroup analyses. Ideally, intervention studies should be designed with the contribution of oncologists, clinical nutritionists, rehabilitation experts, psycho-oncologists, statisticians, and patients [28].

Adolescent and young adults represent a peculiar population of cancer survivors, who deserves specific considerations. They are defined as individuals diagnosed with cancer between 15 and 39 years [29]. The most common cancer types between individuals 15–24 years of age are leukemia, lymphoma, testicular, and thyroid cancers, while melanoma, breast, colorectal, and uterine/cervical cancers are the most common among 25 and 39 years old [30].

Adolescent and young adult cancer survivors express different needs compared to adults and older adults. They are at high risk for adverse metabolic treatment side effects resulting in the early onset of cardiovascular disease, diabetes, metabolic syndrome, and secondary cancer diagnoses [31]. All these comorbidities are associated with increased healthcare costs, but especially with worse QoL and prognosis.

Lifestyle change, in particular, dietary habits, can improve metabolic conditions and prevent the development of comorbidities.

Unfortunately, for this specific population as for other cancer patients' populations, the evidence regarding dietary interventions' efficacy remains largely undescribed and limited. In a recent systematic review including young adults and adolescents cancer survivors, the only four available studies were heterogeneous for age, cancer type, duration, and kind of dietary advice provided [32]. However, the results of this systematic review suggest the high potential to change dietary

behaviors in adolescent and young adult cancer survivors and clearly indicates the need to address the existing nutrition care gaps for a growing and yet understudied population by well-designed clinical trials.

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Survivorship and Palliative Care: First the One, Then the Other?

19

Stefan Rauh

Cancer patients may undergo a series of different phases throughout their life, including active treatment as well as supportive care, survivorship care, and palliative care. Should we have to choose? Are these still different categories?

Historically, in a seminal partly autobiographic paper by Fitzhugh Mullan, the onset of survivorship has been set at diagnosis, with three distinct consecutive phases of "acute" survival (during treatment), "extended" survival (after active treatment, described as a period of "watchful waiting" or "intermittent consolidative treatment) and a final possible phase of "permanent survival" which is synonymous of "cure" without the state prior to diagnosis ever to be completely restored [1]. Still in recent years, our understanding of the pathway of a patient after diagnosis of cancer either led to "curative" or "palliative" treatment, the former potentially leading to cancer-free survival with cure or more or less long treatment-free intervals (Fig. 19.1). The latter would lead to death. The survivorship interval was considered in patients either cured or in chronic conditions with intermitted or continuous treatment [2]. This definition was pragmatic, recognizing the already much described transitional gap between active treatment and follow-up [3]. Patients also rather considered themselves as cancer survivors after a significant disease-free interval [4].

An essential part of survivorship care in the United States is the establishment of a survivorship care plan (SCP). In the American Commission on Cancer 3.3 Accreditation edition, the SCP is centered on patients with curable stages I–III disease, after active treatment. Even though participating institutions are free to include patients with metastatic disease into their local survivorship programs, "patients with Stage ... IV or metastatic disease, though survivors by varying definitions are not required to receive a SCP under Standard 3.3" [5].

Ever since the beginnings of the concept of survivorship care, a holistic approach to the cancer patient has been considered paramount [3]. This approach has

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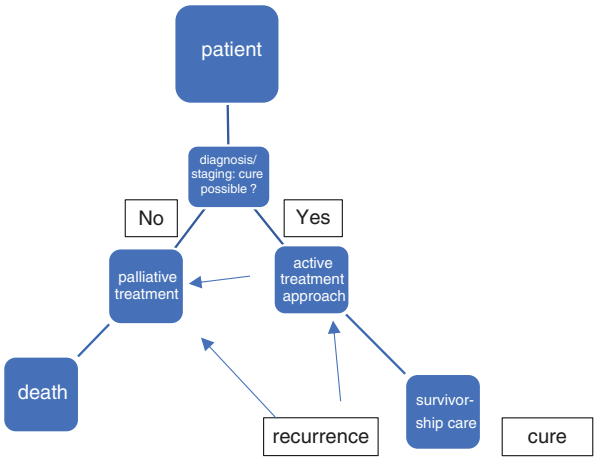

Fig. 19.1 Old model of survivorship—and palliative care

broadened over time as more patient needs have been identified and progressively integrated into survivorship care.

Even in advanced, incurable tumor stages, overall survival has greatly improved in many tumor types during the last decades. More patients may now experience long and possibly repeated periods of treatment-free intervals. Treatment themselves have become less toxic and may provide a far longer response. As an example, immunotherapy with checkpoint inhibitors has led to survival expectancies for formally dismal metastatic melanoma patients to years, while allowing reasonable quality of life [6]. Are these patients not to be considered as survivors—or are they "palliative"? Should they not benefit from a Survivorship Care Plan?

The World Health Organization (WHO) currently defines palliative care as follows: "Palliative care improves the quality of life of patients and that of their families who are facing challenges associated with life-threatening illness, whether physical, psychological, social or spiritual. The quality of life of caregivers improves as well" [7].

This has greatly evolved from its definition in 1990: "Palliative care is the active, total care of patients with progressive, far advanced disease and limited life expectancy whose treatment is not responsive to curative treatment. It refers to the control of pain, and of other symptoms as well as the treatment of social, psychological and spiritual problems" [8].

Palliative care has gradually evolved from end-of-life care to early phases of cancer treatment—with improvements of survival when integrated into a standard approach including active treatment [9], and the assessment of patient-related outcomes [10]. This has led to a general understanding to integrate palliative care early in the treatment setting.

Supportive care is yet another overlapping category of care. The Multinational Association of Supportive Care in Cancer (MASCC) has proposed the following definition of supportive care: "Supportive care in cancer is the prevention and management of the adverse effects of cancer and its treatment. This includes management of physical and psychological symptoms and side effects across the continuum of the cancer experience from diagnosis through treatment to posttreatment care.

Enhancing rehabilitation, secondary cancer prevention, survivorship, and end-of-life care are integral to supportive care" [11].

These overlapping definitions come from different historic positions, but all express the need for holistic cancer care. This has led to the concept and term of "patient-centered care," which was postulated as a European Society of Medical Oncology position paper in 2018. "Patient-centred care should be offered during the continuum of illness, from the time of cancer diagnosis through to survivorship or end-of-life. Needs will evolve together with the disease and anticancer treatment, so ongoing and careful holistic evaluation of requirements should be part of every consultation." The position paper also states that "patient-centred care cannot be standardised, even though it is provided through a standard framework. To ensure that patients can voice their needs, oncologists should incorporate detailed and routine physical and psychological assessments allowing for supportive and palliative interventions to be personalised and integrated in the continuum of care. Patient-reported outcomes (PROs) should be highly encouraged as requesting them has shown to be associated with better QoL, fewer hospitalisations and even increased survival compared with usual care" [12]. In terms of survivorship, the paper strongly encourages oncologists and multidisciplinary teams to provide rehabilitation. The establishment of survivorship care plans is also encouraged, even though the current lack of scientific evidence of its best application into clinical practice [12].

In conclusion, a holistic patient-centered approach should accompany every patient throughout his cancer journey, from diagnosis on (Fig. 19.2). This also fully applies to the survivorship phase which has been broadly discussed in this handbook. Individualizing patient follow-up, detecting his needs over time and provide assistance in a context of varying and limited resources with ever new technologies, is a major challenge on every level, for every individual caregiver as well as for stakeholders on an institutional, national, and global level. Integrative patient care is to begin with the cancer diagnosis, continue throughout survivorship until end-of-life care as a continuum. In oncology, we have made incredible progress over the last

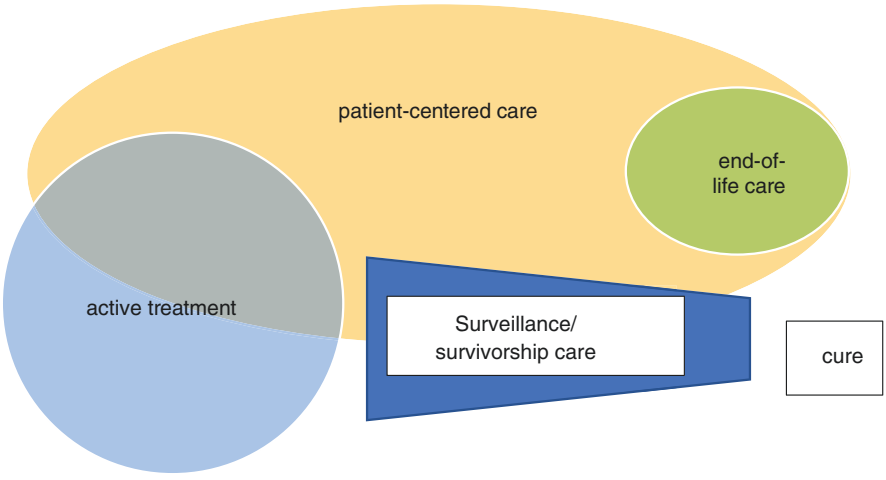

Fig. 19.2 Integrating patient-centered care

decades. We will continue to do so. We will have to make further major efforts to provide this progress within a holistic management: our patients deserve it.

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